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ANALYSIS OF ONE HUNDRED CASES OF SCHIZOPHRENIA WITH RECOVERY

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The literature on recovery from schizophrenia is extensive, but much of it is concerned with statements of outcome at varying lengths of time after hospitalization. A great many such discussions are included under the title of prognosis. Prognosis, however, if it is to mean anything, is not merely a statement of statistical probabilities for recovery but should also include some evaluation of the factors making for recovery, since, when one is confronted with an actual patient, this material is likely to be of greater helpfulness than a conjecture about the future, based on averages which far too often are compiled on such small series of cases as to be valueless.

It was with the hope of organizing the observations of the various authors with specific reference to the factors contributing to recovery that an initial attempt was made to cull the literature on this aspect of the problem of recovery.

There are many good articles on prognosis which touch lightly, or not at all, on the material of this investigation. Lewis [1] concluded that it is difficult to judge the factors concerned with recovery, but expressed the belief that the prognosis is good if there are an abrupt onset, an adequate precipitating cause and a well adapted, nonschizoid personality. Ohta [2] found remissions more numerous among women than among men and predicted a better outcome for patients with pyknic build and acute onset of the disease. The acute onset was also commented on by Gelperin,[3] Braun,[4] Cheney and Drewry [5] and others.

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1. Lewis, A. J.: Prognosis in Schizophrenia, Lancet **1**:339, 1935.

2. Ohta, K.: Zur Prognose der Schizophrenie, Psychiat. et neurol. japon. **39**: 2, 1935.

3. Gelperin, J.: Spontaneous Remissions in Schizophrenia, J. A. M. A. **112**: 2393 (June 10) 1939.

4. Braun, E.: Schizophrenien, Arch. f. Psychiat. **80**: 131, 1927.

(Footnotes continued on next page)

More searching analyses have led to the investigation of personality makeup and other factors within the psychosis. Lemke [6] found a family history of mental disturbance more frequent in the group with the less favorable outcome. Body build and acuteness of onset were not decisive factors. He described the prepsychotic personality of withdrawal, cold affect, paranoid features, etc., and stated that these were less marked in the group of recovered patients. Müller [7] reviewed the results of studies from Kraepelin to Mauz and concluded that the prognosis is unfavorable for patients of asthenic-leptosomatic makeup and prepsychotic schizoid personality with early onset and a basic psychopathologic process in defect and regression. The pyknic and syntonic patients have a better prognosis, the more so if the psychogenic symptoms exceed the expression of a basic process. Sullivan,[8] in a series of three articles, discussed features of malignancy in terms of the psychoanalytic mechanisms present. Kasanin [9] discussed the schizoaffective psychosis and reported the cases of 9 patients who recovered in which there were blending of schizophrenic and affective symptoms, sudden onset, marked emotional turmoil, false sensory impression and a relatively brief psychotic period. The patients were in the twenties or thirties, and usually had a history of a previous attack in late adolescence. They had made a good social and industrial adjustment, displayed interest in life and its opportunities, showed absence of passivity and had come up against specific environmental stress.

There remain a few articles in which the investigators have made a more searching analysis of the underlying factors. Zilboorg's report [10] of reintegration through psychoanalysis in the case of a woman with paranoid schizophrenia is of great interest, particularly his emphasis on withdrawal of affect and its reactivation through analysis. The best American review is still that of Strecker and Willey,[11] and a recent

5. Cheney, C. O., and Drewry, P. H., Jr.: Results of Non-Specific Treatment in Dementia Praecox, Am. J. Psychiat. **95**:203, 1938.

6. Lemke, R.: Ueber Beziehungen zwischen Verlauf der Schizophrenie und ihren encephalographischen Bild, Arch. f. Psychiat. **104**:89, 1935.

7. Müller, M.: Die schizophrenen Erkrankungen, Fortschr. d. Neurol., Psychiat. **7**:447, 1935.

8. Sullivan, H. S.: Schizophrenia: Its Conservative and Malignant Features; a Preliminary Communication, Am. J. Psychiat. **81**:77, 1924; Tentative Criteria of Malignancy in Schizophrenia, ibid. **84**:759, 1928; The Relation of Onset to Outcome in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. (1929) **10**:111, 1931.

9. Kasanin, J.: The Acute Schizoaffective Psychosis, Am. J. Psychiat. **90**: 97, 1933.

10. Zilboorg, G.: Affective Reintegration in Schizophrenias, Arch. Neurol. & Psychiat. **24**:335 (Aug.) 1930.

11. Strecker, E. A., and Willey, G. F.: An Analysis of Recoverable "Dementia Praecox" Reactions, Am. J. Psychiat. **80**:592, 1924; Prognosis in Schizophrenia, J. Ment. Sc. **73**:9, 1927; Prognosis in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. (1925) **5**:403, 1928.

monograph of Langfeld [12] contains discussion of these factors. The most comprehensive review of recent literature is in an article by Blair.[13] We are not primarily interested in his summary of remission rates, wherein it appears that 40 per cent represents an average in all clinics for recovery or improvement of schizophrenic patients not treated by any form of shock.

We are interested, however, in his review of the literature concerning factors considered important in recovery. These appear to be: early age of onset; female sex, pyknic body type; extrovertive temperament; previous history of ability to meet life's problems; exogenic factors in the psychosis, such as rapid onset and catatonic type, short duration of the psychosis, and presence of manic-depressive symptoms.

The pertinent material obtained from these sources and that from the monograph of Terry and Rennie [14] and the articles of Malamud and Render,[15] Stalker,[16] Lewis and Blanchard,[17] Williams and Potter [18] and Gerloff [19] are presented in table 1. It is felt that these articles contain the most searching reviews, although, as the table will show, conclusions are far from unanimous. Scrutiny of table 1 leaves one in a somewhat confused state, since the data are clearly contradictory concerning all the items except the presence of precipitating factors, the acuteness of onset and the personality makeup.

Practically all authors have expressed agreement on the favorable feature of an outstanding disturbing situation acting as a precipitating event in the psychosis. Similarly, the outlook for a very acute psychosis of abrupt and stormy character appears more favorable than that for the slowly progressing, insidious change. The favorable personality is for the most part defined as cyclothymic, not characteristically shut in, with the 1 exception described by Williams and Potter. Concerning all other items findings are decidedly variable.

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12. Langfeld, G.: The Prognosis in Schizophrenia and Factors Influencing Course of Disease, London, Oxford University Press, 1937.

13. Blair, D.: Prognosis in Schizophrenia, J. Ment. Sc. **86**:378, 1940.

14. Terry, G. C., and Rennie, T. A. C.: Analysis of Parergasia, Nervous and Mental Disease Monograph 64, New York, Nervous and Mental Disease Publishing Company, 1938.

15. Malamud, W., and Render, N.: Course and Prognosis in Schizophrenia, Am. J. Psychiat. **94**:1039, 1939.

16. Stalker, H.: The Prognosis in Schizophrenia, J. Ment. Sc. **85**:1224, 1939.

17. Lewis, N. D. C., and Blanchard, E.: Clinical Findings in "Recovered" Cases of Schizophrenia, Am. J. Psychiat. **11**:481 and 513, 1931.

18. Williams, R. R., and Potter, H. W.: The Significance of Certain Symptoms in the Prognosis of Dementia Praecox, State Hosp. Quart. **6**:360, 1920-1921.

19. Gerloff, W.: Ueber Verlauf und Prognose der Schizophrenie, Arch. f. Psychiat. **106**:585, 1937.

Malamud and Langfeld stated that the outlook is better for males, although the prevailing impression is that women do better than men. Data on heredity are inconclusive. The athletic habitus has been stressed by these authors, although the pyknic type of build is usually considered favorable. According to these authors, intelligence and good education would not seem to be significant factors. The majority of investigators

TABLE 1.—*Preponderance of Factors in Cases of*

Author	Sex	Marital Status	Heredity	Habitus	Personality	Intelligence	Environment	Somatic Disturbances	Precipitating Factors
Malamud and Render	M	Married	Tainted	Athletic and normal	Cyclothymic	High (105+)	.....	Acute or chronic physical disease; cerebrospinal fluid permeability decreased	Physical, sexual, economic in particular
Terry and Rennie	..	.....	Absence of taint not an asset	.....	Capacity to socialize; goals adapted to capacity and opportunity	High intellectual level, not an asset	Sympathetic	Temporary infectious process	Onset in situation of strain
Langfeld	M	.....	Equivocal	Athletic and mixed; atypical, with cyclothymic personality	Cyclothymic and atypical personalities	High intellectual level, not an asset; abilities very good	Equivocal	Many exogenic traumas	Many exogenic traumas
Stalker	Not significant	.....	Not significant; aliens, unassimilated	.....	Reaction habits healthy	Education not significant	Outweighing constitutional factors in importance	Tuberculous or focal infections, not significant	Present
Strecker and Willey	..	.....	Absence of taint	.....	Not constitutionally introverted	.....	.....	Toxic and exhaustive	Present
Lewis and Blanchard	..	Single	Not significant	.....	Poor economic and sexual adjustment	Level of education below high school	Stressful families	Inconclusive	Present
Williams and Potter	..	.....	.....	.....	Shut-in	.....	.....	.....	.....
Gerloff	..	.....	Not significant	.....	.....	.....	.....	.....	.....

have noted the presence of somatic disturbances at the onset of the disease as a favorable prognostic feature. Most of the authors have also commented on the presence of affective components, particularly when appropriate or suitable, and the rare occurrence of inappropriate or apathetic affect in the recovered patients. Malamud and Lewis and Blanchard noted that the hallucinations were rarely visual, but this statement was contradicted by Williams and Potter. Good contact and the presence of insight were mentioned as favorable features by Malamud, Terry and Rennie and Williams and Potter.

In summary, therefore, the outstanding features presented by recovered schizophrenic patients seem to lie in the occurrence of an acute psychotic process, adequately motivated, often in the presence of somatic disturbances, which runs a relatively short course characterized by the presence of appropriate affective response and the preservation of contact and insight. The patients for whom the outlook is favorable are

Schizophrenia with Recovery Reported in Literature

Previous Attacks	Age of Onset	Span of Onset	Course	Subsequent Attacks	Affect	Motor Disturbance	Hallucinations	Confusion States	Contact; Rapport; Insight
Previous nonschizophrenic attacks	Second and fourth decades	Acute	Stormy; improvement in hospital	.....	Inadequate and inappropriate rather than apathetic	Overactive; resistive	Visual rare	Present	Present
.....	.....	.....	.....	.....	Affective admixtures present	Personal appearance and habits intact			Rapport; will to cooperate; desire for help expressed
.....	.....	Comparatively acute	.....	.....	Atypical, especially manic-depressive features				.....
.....	.....	Acute	.....	.....	Well retained and appropriate	Hallucinations not significant; atypical, especially manic-depressive features			.....
.....	.....	Abrupt; stormy	.....	.....	Suitable	.....	.....	.....	.....
.....	.....	None over 2 years	Gradual or irregular	1%	Present in 27% (depressive)	Mannerisms; negativism; stupor	Auditory in 69%	.....	.....
.....	.....	.....	.....	.....	Consistent and adequate	.....	Absent except perhaps for visual	.....	Insight present
.....	Early	.....	Acute	More cures after subsequent attacks	.....	More prominent than disturbances of affect	.....	.....	.....

those of relatively outgoing makeup, pyknic or athletic body build and average, not necessarily superior, intelligence or education.

The purpose of this study is to submit these conflicting observations to careful scrutiny in the analysis of a selected group of 100 cases of schizophrenia in which the patients recovered. After a careful preliminary review of all the material, it was deemed advisable to include many other features presented by the patients and by their environment which might be considered important in the evaluation of the recovery process. The material to be presented, therefore, will deal with a large

variety of items, selected in part from the pertinent literature on the subject, but to an equal extent from a consideration of all factors which might enter into the experiment of nature. The discussion to follow, therefore, will revolve around the following specific items:

Prepsychotic Factors

1. Sex
2. Marital status
3. Heredity
4. Physical habitus
5. Personality makeup
6. Intelligence and educational level
7. Presence of outstanding sexual factors
8. Nature of environment
9. Precipitating factors

Course of Psychosis

10. Previous attacks
11. Age of onset of psychosis
12. Span of onset of psychosis
13. Course and duration of psychosis
14. Subsequent attacks
15. Psychotic picture
    - (*a*) Somatic condition at time of psychosis
    - (*b*) Affective admixtures
    - (*c*) Motor disturbances
    - (*d*) Frequency and type of hallucinations
    - (*e*) States of confusion
    - (*f*) Contact
    - (*g*) Disordered thinking
    - (*h*) Frequency and type of delusions
    - (*i*) Hypochondriasis or somatic delusions
    - (*j*) Negativism
    - (*k*) Mannerisms
    - (*l*) Panic and excitement
    - (*m*) Stupor
    - (*n*) Passivity
    - (*o*) Ideas of influence
    - (*p*) Insight
    - (*q*) Tests for thinking disturbances
16. Subsequent attacks
17. Degree to which the psychosis is understandable in terms of the prepsychotic life problems and general modes of reacting
18. Factors outside of hospital which may have contributed to recovery
19. Duration of recovery
20. Prognosis at discharge in relation to outcome

MATERIAL

Out of approximately 1,200 cases of the parergasic reaction type (schizophrenia) thus far studied in the catamnestic project of the Henry Phipps Psychiatric Clinic, 100 have been selected in which recovery was obtained without the use of shock therapy and was maintained for from

five to twenty-five years. By this is meant that when there was a relapse the duration of the subsequent recovery has been at least five years.

The parergasic picture is a highly individual one, not easily classifiable into any simple categories. The many varieties of the picture have been adequately described previously in a monograph on parergasia from this clinic.[14] Any one working with a large series of schizophrenic patients is forced to realize that the simple kraepelinian differentiations of catatonic, paranoid, hebephrenic and simple are too rigid and lacking in plasticity for any worth while attempts at classification. However, since almost all previous reports on outcome or recovery deal with the material in these four categories, we have sorted out our cases whenever possible into these four major reaction groups. No attempt was made to force any case into one of these categories, but certain outstanding features of the illness made it possible to do so in most cases, with certain broad generalizations. There remains, however, a group of 16 cases (7 men and 9 women) in which the material could in no way be fitted into

TABLE 2.—*Method of Follow-Up Study of One Hundred Patients*

	No. of Patients	
Social service interviews only	6	
Letter only (many from family physician)	28	
Physician's interviews only	9	Total number seen by psychiatrist 60
Physician's interview and letters	27	
Physician's and social service interviews	18	
Physician's interviews, social service interviews and letters	6	
Social service interviews and letters	6	

the kraepelinian nosology. The condition in these cases is, in our opinion, clearly schizophrenia, but of an undifferentiated type.

In this study of 100 cases of schizophrenia with recovery, the follow-up material has been obtained by personal interview in 72 instances and by letter in 28, as is shown in table 2.

In each case we chose to speak of recovery when we had evidence that the patient had been able to resume work or other productive activity, to present an appearance to family or friends that seemed in no way unusual or abnormal and to show adequate interest in his own appearance and status. In some cases the patient married and led a normal life, and in many others he reported that he was better than he had ever been previously. In some instances the family stated that the patient was keener and more mellow than before, that he had a new personality, etc. In no case have we considered the patient recovered if his behavior was in any way disturbing or obviously unsocial or if he expressed ideas that were psychotic or related to the acute phase of his illness. In each case the patient has been described as "well," "as well as formerly" or "better than formerly."

Of approximately 1,200 cases reviewed, 192 were singled out as representing recoveries. In these 192 cases there were 111 women and 81 men. These 192 cases were scrutinized meticulously with a view to excluding any in which the diagnosis was not clear or the recovery questionable. The result consists of 100 cases in which recovery was considered unequivocal. For statistical purposes, an arbitrary 100 cases was decided on, divided equally among 50 men and 50 women. These figures give no indication of the percentage of complete recoveries, but in an earlier presentation [20] one of us [T. R.] showed that at the end of a long period of observation 24.56 per cent of the schizophrenic patients in the clinic had shown complete recovery. Cases in this study represent patients similar to those who in the former study were classified as completely recovered.

Twenty women (1 divorced) and 12 men had been married at the time of admission to the hospital.

TABLE 3.—*Clinical Grouping of Recovered Patients*

Type of Schizophrenia	Men	Women	Total
Catatonic	10	14	24
Paranoid	19	17	36
Hebephrenic	12	9	21
Simple	2	1	3
Unclassified	7	9	16

Since the selection of the patients was based entirely on recovery and not on the clinical reaction, it should be of interest to see into what clinical groups they fall. Table 3 shows the distribution.

Thus it will be seen that the largest number of recovered patients were recruited from the paranoid group and the next largest from the catatonic.

Status According to Sex.—Since 50 women and 50 men have been selected arbitrarily, the sex incidence does not play a part here. However, of the original 192 cases selected on the criterion of recovery alone, 111, or 57 per cent, were women. In the preliminary study of the schizophrenic material of the Henry Phipps Psychiatric Clinic, it was found that of the 500 patients studied 45 per cent were males and 55 per cent females. Twenty per cent of the total number of males and 27 per cent of the total number of females eventually recovered. These figures show a somewhat more favorable prognosis for females.

It is our opinion, based on the results of the total study, that the factors are so nearly alike in the cases of males and of females that no legitimate differentiation can be observed between the two groups. Thus, the personality structure, the character of the illness and the course of the disturbance are so nearly alike in men and in women that no attempt

will be made in the discussion to consider the sex factor separately. The incorporated tables, for the most part, show the patients grouped as males and females for the interest of any one who wishes to scrutinize the material further from the standpoint of sex.

Duration of Recovery.—All the patients have maintained recovery for at least five years—55 for over eleven years, 24 for over sixteen years and 3 from twenty-one to twenty-five years.

ANALYSIS OF THE PREPSYCHOTIC PICTURE

In any pluralistic concept of man, one is obligated to consider all the factors that make a difference in the person's heredity, original constitutional endowment and subsequent environmental experiences. One's search, therefore, extends to the understanding of that which is going on within the patient, his somatic function, his general personality function, his intellectual endowment and the role it plays, the general organization of the drives and activities and emotional makeup, the development of the sexual life and the personal and more general social adaptations. Outside the patient himself, one must consider the role played by environment and external events, either as precipitating factors or in the continuation of the disturbance.

Heredity.—In dealing with the patient's heredity, we considered as a "taint" the occurrence of any psychotic condition in sibs, cousins, parents, aunts, uncles or grandparents. When there existed in these relatives noticeable oddities, alcoholism, criminal tendencies or other personality difficulties of a disturbing nature, although not to be regarded as actually psychotic, the hereditary picture was considered mixed. In nearly one third of the recovered patients in this series no psychotic hereditary taint was found. Over half of them (53 per cent), however, presented a family history of psychosis. For 1 patient no family history was obtainable. Of the 53 patients with hereditary taint, 12 (22.6 per cent) gave a family history of schizophrenia and 22 (41.5 per cent) one of affective psychosis, 1 of the latter having a family history of both disorders.

Since control material is needed in order to determine the significance of these findings, we may compare these 100 cases with the group of 500 unselected cases used in a previous follow-up study,[20] in 40 per cent of which (39 per cent of the males and 41 per cent of the females) we found a family history of psychoses. The incidence in the recovered group seems, therefore, significantly higher. Of definite significance is the finding of a schizophrenic heredity in 22.6 per cent of those patients having a positive hereditary factor, whereas in the unselected group of

20. Rennie, T. A. C.: Follow-Up Study of Five Hundred Patients with Schizophrenia Admitted to the Hospital from 1913 to 1923, Arch. Neurol. & Psychiat. **42**:877 (Nov.) 1939.

500 cases a similar heredity appears in only 9.9 per cent. Similarly, the incidence of affective disturbances in the tainted heredity is much higher in the recovered group (41.5 per cent) than in the unselected group (14.8 per cent).

One might conclude, as has been done in some of the studies reported in the literature in which a similar preponderance was discovered, that since over half the recovered patients showed a tainted heredity this is a favorable factor for recovery. It may be that a constitutional predisposition renders such persons more liable to a psychosis, which can then be viewed as of less serious significance.

Habitus.—Unfortunately, the records of only 27 of the group of recovered patients contained a specific statement about the habitus. In these, however, the types recorded are as follows: asthenic, 13; athletic, 7; pyknic, 2; dysplastic, 2; asthenic-athletic, 2; pyknic-athletic, 1. These data cannot be considered to represent the entire group but are in accordance with the usual preponderance of the asthenic makeup among schizophrenic patients. We do not feel warranted, on the basis of the few records available, in concluding that the psychosis in the asthenic type has a more favorable prognosis.

Personality.—The schizophrenic personality was described in the previous study of a group of 500 cases. The schizoid personality, which has been the object of considerable investigation, is designated in the meyerian pattern as egotropic and is recognizable as belonging to the person who socializes with difficulty, who tends to substitute his own inner world for objective reality, who may be sensitive or sexually unadjusted or whose manner may vary from irritable and explosive, aggressive, unsympathetic or haughty to timid, submissive or apathetic.[21] In the clinical records we find such descriptions as these:

Timid, submissive, sensitive, cheerful, religious, attached to mother.

Egocentric, selfish, sensitive, stubborn, daydreamer, attached to parents and siblings.

Very sensitive, quiet, lacking in self confidence, friendly, submissive, conscientious, religious.

Ambitious, given to dislikes, headstrong, having few friends, quiet, quick tempered.

Seclusive, daydreaming, ambitious, sensitive, irritable, having few friends, persevering, nonconfiding, sensitive to criticism.

Shy with women, seclusive, sensitive, precocious, tenacious of ideas that bolster self esteem, argumentative.

Retiring, unaggressive, having no interest but work, impulsive in changing jobs, even tempered, sociable.

21. Muncie, W.: Psychobiology and Psychiatry, St. Louis, C. V. Mosby Company, 1939.

Timid, morose, daydreaming, unsociable, untruthful, subject to tantrums as a child, not industrious.

Brooding, poor mixer, retiring, seclusive, abnormally attached to family, having few girl friends, labile.

We find that the parergasic picture, however, occasionally appears in the "outgoing" or syntropic, personality, and sometimes in a mixture of the two types. In this study two thirds (66 per cent) of the group of recovered schizophrenic patients presented a preponderantly schizoid prepsychotic makeup. Nearly one quarter of them were syntropic in their response, and only about one tenth showed a mixture of the two types. In contrast, in the undifferentiated group of 500 cases, 55 per cent of the patients showed a preponderantly schizoid makeup. This higher incidence in the recovered group might, therefore, indicate that the development of a psychosis in a person with a typical schizoid makeup has a less serious prognostic implication than the appearance of a similar psychotic picture in a person with a nonschizoid background. A study of the four major clinical groups shows no outstanding difference in personality makeup among patients with the catatonic, the paranoid, the hebephrenic and the simple type, although there is a suggestion that the typical schizoid makeup is less common in the catatonic group.

Intelligence and Education.—A high percentage of our patients represent persons of superior educational background. This, in part, undoubtedly represents selective criteria of admission to the clinic. The distribution according to education is shown in the tabulation.

	Below High School	In High School	High School Graduate	High School +	B.A. Degree or Higher
Females	21	3	15	5	6
	42%	6%	30%	10%	12%
Males	17	4	11	1	17
	34%	8%	22%	2%	34%
Total	38	7	26	6	23
	38%	7%	26%	6%	23%
Totals for unselected group of 500 patients	35%	19%	12%	14%	20%

Of these 100 recovered patients, therefore, the largest single number were persons of poor scholastic background. This may point to the fact that a psychosis occurring in persons of limited intelligence or poor education is prognostically more favorable, perhaps because the illness itself is less alien than similar manifestations would be in a person of good intelligence and training. The preponderance of the number of patients of the limited education group is not due to the youth of the group, since the majority of the patients had the onset of their psychosis between the ages of 21 and 30.

A comparison with the unselected group of 500 patients, however, reveals no such significant difference in respect to this factor as is shown in the preceding tabulation.

Sex.—Three fourths (74 per cent) of the recovered patients had shown difficulties in sexual adjustment prior to their illness. These comprise a great variety, examples of which are enumerated in the following list:

Males:

- Worry about masturbation since age of 9; ejaculatio praecox; relations with prostitutes, with remorse
- Homosexuality
- Heterosexual perversions
- Perversions with animals
- Marital dissatisfaction: contraceptive measures; frigidity of wife; impotence
- Delusions of small genital organ
- Disgust after first attempt at sex relations
- Fear of venereal disease
- Anal eroticism
- Fear of impotence after hernia; shame at wearing truss
- Illicit sex relations, with remorse or worry

Females:

- Illicit sex relations, with remorse
- Infatuation with men
- Dissatisfaction with use of contraceptives
- Religious worry due to use of contraceptives
- Reaction to menarche concerning which the patient had no information, or misinformation (tension and fear)
- Resentment toward menstruation
- Fear of pregnancy when single, or when married
- Sex episode in childhood, with punishment
- Masturbation in childhood, with punishment and shame
- Homosexuality
- Disappointment in love, with or without sex relations
- Arousal by physician
- Dislike of sex relations in marriage, in case of a frigid or of a nonfrigid woman
- Autistic and semiautistic sex fantasy life
- Humiliation caused by desertion of husband

Sexual difficulties were more frequent in the paranoid group. In the previously studied group of 500 unselected patients, comparable difficulties were found in 72.8 per cent. The group of recovered patients, therefore, does not differ materially in respect to this factor.

Environment.—Over half the patients (54 per cent) had a definitely unfavorable environmental background which was contributory to the illness. This was significantly higher than in the undifferentiated group in which 41 per cent had an unfavorable environment. In many cases, also, the unfavorable factors in the environment became the acute precipitating situation leading to the onset of the psychosis.

Some of the unfavorable environmental factors under which the patients labored were:

Alcoholic father and psychotic mother
"Rigid" family
Dominating mother
Living with indifferent in-laws
Monotonous, frustrated or lonely life
Living amid unfair competitions
Family disharmony
Homosexual environment in college, in a case of latent homosexuality
Life in an orphanage
Responsibilities in the case of a person with a dependent personality
Brutal husband
Mixed religious marriage, with worry
Religious oddities and emotionalism
Lack of father with oversolicitious and dominating mother
Unfriendly wife and in-laws

Factors which were clearly shown to precipitate the disturbance are enumerated as follows:

Environmental difficulties
Alcoholic father, psychotic mother
"Rigid" family
Dominating mother
Living with unsympathetic in-laws
Narrow life, no outlet for talents
Family friction
Narrow life
Uncongenial home, with responsibility and worry; family disharmony
Family dominating and with tendency to depression, homosexual school environment, in a case of latent homosexuality
Only child, away from home for first time
Institutional (orphanage) life since age of 8
Unaccustomed responsibility
Brutal husband
Stressful family
Discordant, unsympathetic family
Mother with tendency to depression, eventually suicided
Early death of only confidant (father), with money worry
Family difficulty after death of mother
Stressful family, with unfavorable conditions of employment
Unfriendly wife and in-laws
Nervous family, outstripped by brother
Father with tendency to depression, dominating mother
Parents with tendency to depression, father eventually suicided
Patient a posthumous son, with dominating mother
Psychotic family (4 cases in which this seemed a factor by itself)
Orphan since age of 9, marital frustrations
Family overreligious with tendency to depression
Father irritable, mother unfaithful, family destitute

Incidents which were acute precipitating factors in the psychoses were:

Overwork at puberty
Disappointment in love (several patients)
Sex experiences, social worries
Worry over job or over broken engagement
Indecision over job
Disabling disease
Difficult job
Bereavement
Syphilis in homosexual partner

In some cases (17 per cent) the environment was closely linked with the predominating factor in precipitating the illness. The details of these individual difficulties are listed as follows:

Environmental Situation	Precipitating Factor
Habitual promiscuity	Fear of pregnancy and disappointment in marriage
Living under unfair competition (love)	Disappointment in love
Mixed marriage, with conflicts	Contraceptive-religious worry; dissatisfaction with sex life
Seclusive life with sick mother; poverty	Semiautistic love for attending physician
Gossiping, small town life	Disappointment in marriage, with feeling that every one knew
Widowed life; narrow interests	Loss of both her grown children
Loveless marriage; superficial interests	Kiss by physician
Humiliating desertion and divorce; small town life; dominating mother	Failure of second love affair
Loveless marriage; neglectful husband	Incomplete psychoanalysis
High-strung family; complicated social life	First illegitimate coitus, with fear of pregnancy
Exotic religious beliefs	Religious disputes after loss of job
No father since age of 8; oversolicitous mother	Poor judgment at outset of career
Mental illness in family; money worry	Conflict between money making vs. desired profession
Medical competition with poverty	Selling of small family-owned hospital; mental illness of brilliant brother
Late marriage; jealousy of disliked stepdaughter	Loss of investment led to fear of loss of affection
Marital disharmony; interfering in-laws	Impending unwanted divorce

Summary.—Consideration of the foregoing material shows clearly that the constitutional factor in these patients is an important one. Precipitating events and environmental situations play a significant role.

Significant in recovery from parergasia, therefore, is the high incidence of a family history of the disease, with a predominance of affective disturbances, but with an additional high frequency of schizophrenic psychoses. The schizoid makeup predominates.

In scrutinizing the factors according to their distribution in clinical groups, it would appear that the catatonic group shows a proportionately small number of persons with typical schizoid makeup, that sexual factors emerge more commonly in the paranoid group, as do also disturbing environmental situations. The catatonic group, however, shows the highest incidence of disturbing acute precipitating factors. Table 4 presents the actual data thus far considered.

TABLE 4.—*The Prepsychotic Picture*

Type of Schizophrenia	Heredity				Habitus						Personality			Intellectual Level					Sexual Factors	Environment	Precipitating Factors
	Psychotic	Nonpsychotic	Minor Deviations	Not Known	Asthenic	Athletic-Asthenic	Athletic	Athletic-Pyknic	Pyknic	Dysplastic	Schizoid	Outgoing	Mixed	Below High School	In High School	High School Graduate	High School Plus	B.A. Degree or Higher			
Females																					
Catatonic.....(14)	5	6	3	..	1	..	1	..	..	..	10	3	1	8	3	2	0	1	10	9	5
Paranoid.....(17)	9	7	..	1	..	..	1	1	..	..	8	8	1	9	0	5	0	3	14	10	6
Hebephrenic.....(9)	6	1	2	..	1	..	1	..	..	..	7	0	2	2	0	2	4	1	6	3	0
Simple.....(1)	1	..	..	..	..	..	..	..	..	..	1	..	..	1	..	..	..	..	0	0	0
Unclassified.....(9)	3	4	2	..	1	..	1	..	..	..	8	1	0	1	..	6	1	1	8	4	7
	24	18	7	1	3	..	4	1	0	0	34	12	4	21	3	15	5	6	38	26	18
Males																					
Catatonic.....(10)	6	4	0	..	3	1	..	..	..	..	8	1	1	3	0	4	1	2	5	4	4
Paranoid.....(19)	11	2	6	..	2	1	2	..	1	2	10	5	4	5	3	1	..	10	15	12	3
Hebephrenic.....(12)	5	6	1	..	3	..	1	..	1	1	8	3	1	5	1	4	..	2	9	6	3
Simple.....(2)	2	..	..	..	..	..	..	..	..	..	1	1	..	..	..	..	..	2	2	2	0
Unclassified.....(7)	5	2	..	..	2	..	..	..	..	..	5	1	1	4	..	2	..	1	5	4	2
	29	14	7	0	10	2	3	..	2	3	32	11	7	17	4	11	1	17	36	28	12
	53	32	14	1	13	2	7	1	3	3	63	23	11	38	7	26	6	23	74	54	30

ONSET AND DURATION OF THE PSYCHOSIS

Previous Attacks.—Of these 100 patients, 20 of the women and 14 of the men (34 per cent of the group) had had previous disturbances. Of these, 2 of the women and 1 of the men had required brief hospitalization (1 for a suicidal, 1 for a paranoid-delusional and 1 for a psychotic episode). The prevailing disturbances were: hypochondriasis in 5 patients; anxiety in 8; obsessive-compulsive psychosis in 5; depressions in 5; chorea in 3; delusional episodes, in 4; accompanied hallucinations, in 2; stammering, in 1; fainting attacks, in 1; and episode of unreality, in 1.

Age of Onset.—The greatest incidence of onset (40 per cent) in this group, like the 51 per cent in the larger group (previously studied) with all types of outcome, lies between the ages of 21 and 30. In the present

TABLE 5.—*Ages at Onset of Schizophrenia in a Group of Recovered Patients and a Group of Unselected Patients*

Type of Schizophrenia	Age of Onset: Under 20	21-30	31-40	41-50	Over 50
A. One Hundred Patients Who Recovered					
Females					
Catatonic	4	5	4	1	..
Paranoid	0	9	5	3	..
Hebephrenic	6	3	..	..	..
Simple	1	..	..	..	..
Unclassified	3	1	5	..	..
Total number of females	14 (28%)	18 (36%)	14 (28%)	4 (8%)	..
Males					
Catatonic	4	4	1	..	1
Paranoid	4	7	6	2	..
Hebephrenic	4	7	0	1	..
Simple	..	1	1	..	..
Unclassified	2	3	1	1	..
Total number of males	14 (28%)	22 (44%)	9 (18%)	4 (8%)	1(2%)
Males and females	28 (28%)	40 (40%)	23 (23%)	8 (8%)	1(1%)
B. Five Hundred Patients with All Types of Outcome					
Females	19%	50%	23%	7%	0.2%
Males	26%	53%	13%	7%	0.6%
Males and females	21%	51%	20%	7%	1.0%

TABLE 6.—*Span of Onset of Psychosis*

Course		Females	Males	Both
Acute onset (less than 6 mo.) with recovery within	6 mo.	13	12	25
	1 yr.	10	9	19
				44%
	2 yr.	3	2	5
	3 yr.	1	0	1
	4 yr.	0	1	1
	5 yr.	3	1	4
	7 yr.	0	1	1
	9 yr.	0	1	1
		30	27	57
Gradual onset (more than 6 mo.) with recovery within	6 mo.	7	6	13
	1 yr.	1	3	4
	2 yr.	3	3	6
	3 yr.	0	2	2
	4 yr.	0	2	2
		11	16	27
Acute onset with recovery within 6 mo. with recurrence		6	6	12
Acute onset with recovery in more than 6 mo. with recurrence		2	0	2
				14
Gradual onset with recovery within 6 mo. with recurrence		1	0	1
Gradual onset with recovery in more than 6 mo. with recurrence		0	1	1
		9	7	16
		50	50	100
Number of patients with 1 recurrence		8	5	
Number of patients with 2 recurrences		1	2	
Number of patients with more than 2 recurrences		0	0	
		9	7	

group, however, 28 per cent (as compared with 21 per cent of the 500 schizophrenic patients) had the onset of their disturbance before the age of 21. This group of recovered patients, therefore, shows more persons with onset of the disease in the younger decade than does a similar unselected group of schizophrenic patients. These findings are shown in table 5.

Span of Onset.—The length of time from the point at which the patient showed definite psychobiologic difficulty and that at which the actual onset occurred and he was unable to carry on his former activities cannot be indicated satisfactorily in a summary. The average of the spans for all the patients, moreover, is misleading (men, twelve and one-fourth months, and women, eight and a half months, as compared with thirteen and a half months for the group with all types of outcome). The durations of onset for this series of recovered patients ranged from one week to twelve years. The latter figure is for a paranoid woman. The next greatest span was that of seven years, occurring in each of 2 paranoid men. The other member of the group with a span of onset lasting more than five years was a hebephrenic man, with a span of six years, who also had delusions of persecution. It is striking, however, that 71 per cent of these patients had an acute onset of illness of less than six months' duration. Table 6 shows the facts concerned with onset.

Course.—The course of the process from the beginning of difficulty to recovery is also too individual and varied to lend itself easily to summary. Twenty-five per cent of the patients who recovered had a duration of onset of less than six months and recovery within six months with no recurrence. An additional 19 per cent had a duration of onset of less than six months and recovery within a year. Twenty-seven with a duration of onset of more than six months eventually recovered, nearly half before six months had passed. These patients also had no recurrences. When those who had later relapses and recovery are included, it is found that 71 per cent of the patients had a duration of onset of less than six months.

In all, 51 patients recovered within six months, although of these 14 had subsequent recurrence before ultimate recovery. Thus it is seen that the group of recovered patients is characterized by a short span of onset and a short period of hospitalization.

Subsequent Attacks.—Sixteen of the 100 patients had a relapse during the period following their discharge from this clinic. Of these 16, 2 women were among those who had had previous attacks, although not severe enough to require hospitalization. Of the patients who suffered

relapses, 8 women and 5 men had one recurrence. One man and 2 women had two recurrences, but none of the 100 patients had more than two recurrences. Table 7 shows the incidence of both previous and subsequent attacks.

The hebephrenic and paranoid gave a history of more previous attacks; the catatonic patients were found to have more subsequent attacks before final recovery.

STUDY OF THE PSYCHOTIC PROCESS

Somatic Conditions.—Thirty-five per cent of all the patients who recovered showed somatic disturbances during the onset or at the time of illness. This proportion is significantly higher than that in the undif-

TABLE 7.—*Incidence of Previous and Subsequent Attacks*

Type of Schizophrenia		Previous Attacks	Subsequent Attacks
Females			
Catatonic	(14)	6	4
Paranoid	(17)	7	2
Hebephrenic	(9)	3	1
Simple	(1)	0	0
Unclassified	(9)	4	2
		— 20	— 9
Males			
Catatonic	(10)	2	1
Paranoid	(19)	3	2
Hebephrenic	(12)	7	2
Simple	(2)	1	0
Unclassified	(7)	1	2
		— 14	— 7
Males and females		34	16

ferentiated group, in which the same factors were present in 22 per cent. The somatic factors present are enumerated as follows:

Males

Calcified pineal gland; generalized enlargement of thyroid; diabetic dextrose tolerance curve
Pulmonary tuberculosis
Hypertension; cardiac hypertrophy
Trace of globulin in cerebrospinal fluid; blood pressure 162/98 (age 26)
Osteomyelitis
Repair of hernia with testicle in abdomen
Recent pneumonia
Recent prolonged typhoid fever
Hernia
Ten cells and globulin in cerebrospinal fluid
Asthma and rose colds
Basal metabolic rate —22 per cent; weight 221 pounds (100.2 Kg.)
Influenza just before admission
Pituitary disorder

Females

Influenza before admission
Chronic nephritis; hemoglobin 45 per cent
Pseudo angioneurotic edema
Toxic goiter
Unexplained rise and fall of temperature above normal
Tonsillitis
White blood cells 16,320; increase unexplained
White blood cells 12,160 (acute tonsillitis)
Lacerations with pelvic pain for past two years, since childbirth
Pyelitis (temperature 104 F.)
Mitral stenosis; cardiac hypertrophy; thyroid adenomas
Influenza before onset
Chronic sinusitis
Basal metabolic rate — 19 per cent
Pulmonary tuberculosis
Myxedema; basal metabolic rate from + 30 to — 20 per cent
Epileptic convulsions
Mild hyperthyroidism
White blood cells 15,700; increase unexplained
Slight deafness since age of 18 (present age 37)
Bromides 200 mg. per hundred cubic centimeters of blood on admission

A woman with a catatonia had a hyperthyroid condition and made a quick recovery after lobectomy.

According to Muncie,[21] the schizophrenic patient, in his parergasic type of reaction, exhibits disorders in his rapport, in his thinking processes and talk, in affect, in content, in motility and in intellectual assets. In the study of this group, therefore, the preponderance of these disorders has been noted.

Affect.—A display of affect occurred in 63 of the cases. This does not refer to mere laughter or crying, both of which occur frequently in the schizophrenic patient in situations which are completely neutral or even in which the reverse response is indicated, and which, moreover, cannot be explained by the patient or may even be announced to be beyond his control. To be considered as affective manifestations, the laughter must be infectious or be the expression of emotional pleasure or the weeping must be accompanied by suitable facies and manner, sense of guilt or statement of depressive mood. Mere worry, or sometimes even hopelessness, does not convey a thymergasic feeling. Suicidal attempts may be the response to hallucinatory commands in which no trace of depression can be found, or they may be made in attacks of panic with fear of torture. These attempts do not in themselves establish the presence of affect. The presence of rhyming, flight, punning or playfulness, in contrast to mere silliness, and the expression of self accusations, sense of responsibility, genuinely doleful weeping or consistent depressive statements lead one to look for the accompaniment of affect.

Classification as Schizophrenic and Affective Features.—This does not mean that the display of affect predominated in any of these patients; if affective features had been preponderant, the patient would have been classified with the affective group showing schizophrenic features. In the case of very few (15 per cent, or 10 women and 5 men) was the diagnosis even schizophrenia with affective features. Each of 33 women and 30 men, however, displayed at some time during their illness a capacity for genuine affect. Of 19 of the group, 11 showed occasional incongruous affect. Only 36 per cent (36 patients) were reported as showing no adequate affect throughout their illness. Of these 36, 8 showed incongruous affective response.

One must bear in mind that this does not mean that the affect was predominant or even present, throughout the illness. It does mean, however, that these patients showed at some time or another, briefly, the capacity for responding with affective expression. This is, of course, a striking observation on these patients who recovered and must mean that the preservation of appropriate affective response is an important factor in the subsequent recovery.

Motor Disturbance.—The motor disturbances occurring in 37 men and 35 women (total, 72 patients) consisted of impulsive hitting or smashing; screaming; stereotyped chanting (even between gulps of food); stereotyped use of words, phrases or movement, or even masturbation in a rhythmic manner; stilted talking and walking; reptilian withdrawal; imitative repetition of words or motion; attempts at self beating or mutilation, hanging, as from a cross, or other symbolic behavior; running from the house at the onset in insufficient or no clothes; meaningless activity; grimacing; spitting; whirling; tense and strained behavior; assaults; restless overactivity; pulling the sheet or other cloth over the head; mirror gazing; jerking; smearing and various other kinds of untidiness with excreta.

Hallucinations.—Of these 100 patients, 67 per cent displayed hallucinations, of which the auditory were in predominance; the latter either occurred alone (29 per cent) or were accompanied by visual hallucinations (24 per cent), or both auditory and visual hallucinations were accompanied by the olfactory (4 per cent) or the tactile (1 per cent) type. The hallucinations of hearing, therefore, were evident in 58 patients (27 males and 31 females). These patients, for the most part, heard voices instructing them to perform some of the various acts described. However, some of them heard signals, bells, music, chirpings, shots or buzzings. Some of the voices heard were cursing, accusing, ridiculing, promising, proposing, inviting or commanding suicide, sacrifice or submission. There were threats of impending torture or death, information on infidelity of the spouse and similar ideas. These voices

might originate from outside the building, from the walls, the pillow, the corners of the room, from the patient's throat or abdomen or from within the head. They might belong to God, Napoleon, the physician, the spouse, the sweetheart or the police. Two patients heard "their own thoughts" in different parts of the head. Another heard all sounds amplified.

Of the visual hallucinations entertained by these patients, many were visions of God, spirits, angels, eyes, moving sky, objects appearing and disappearing, faces in trees, "obscene faces," burning buildings, animals (often terrifying), lights, figures, etc. Two patients announced that they saw voices. Some had hypnogogic hallucinations, which might be terrifying, before falling asleep.

The olfactory hallucinations were those of food, gas or ether. The tactile ideas were of the touch of the hand of the dead husband or daughter.

Thirty-three patients were not hallucinated. Since Bleuler placed hallucinations as one of the cardinal secondary symptoms of schizophrenia, this is a surprisingly large number in whom the hallucinatory phenomenon was absent.

Confusion.—This is a general term, too vague to be of much specific importance. In the older literature, however, one finds frequent references to confusion, without adequate definition. We have included under this term any behavior which seemed purposeless, mixed up or not leading to a constructive goal, particularly when the patient at the same time spontaneously complained of being perplexed, hazy, mixed up or confused. Thirty-nine patients were not able to put on their clothes correctly, could not find their beds or performed other acts of a confused state. Eight women and 2 men expressed the feeling of being puzzled or perplexed.

Contact.—In only half of the patients (51 per cent) was the ability to establish contact seriously interrupted, and in them only at various intervals throughout the illness. Thus in most of the patients it was possible to establish a workable relationship. A few were incoherent throughout their stay and recovered after discharge. Some had periods of inaccessibility. Many were able to discuss neutral topics even before they were led to abandon their delusions. Most of them would usually give some attention to the physician's attempt to reach them, and good contact was established. Some even showed excellent rapport soon after admission and throughout the illness.

Conclusion.—Table 8 shows the incidence of affect, affective features, motor disturbances, hallucinations, confused states and defective contact.

A survey of the items included in table 8 shows no significant differences in the occurrence of somatic disturbances in the clinical groups.

A proportionately larger number of the catatonic patients presented an affectively tinged picture; yet this group had the largest number of patients exhibiting difficulty in establishing contact. The hebephrenic patients as a group showed a proportionate decrease in the occurrence of hallucinations.

Outstanding in these recovered patients were the somatic difficulties, a strong affective tinge and the maintenance of rapport and ability to establish contact, which were noted in half of them. Hallucinations were predominantly of the auditory variety, but were absent in 33 cases.

TABLE 8.—*Incidence of Various Affective, Motor and Intellectual Disorders*

Type of Schizophrenia	Somatic Pathologic Condition	Affect	Motor Disturbances	Total Number of Hallucinations	Hallucinations						Confusion States	Defective Contact
					Auditory	Visual	Auditory plus Visual	Auditory plus Olfactory	Auditory plus Tactile	None		
Females												
Catatonic.....(14)	5	11	11	(13)	3	4	6	0	0	1	9	10
Paranoid.....(17)	8	11	14	(12)	6	1	4	1	0	5	5	9
Hebephrenic.....(9)	2	6	5	(5)	1	2	1	1	0	4	4	2
Simple.....(1)	0	0	0	(0)	0	0	0	0	0	1	0	0
Unclassified.....(9)	5	5	5	(8)	4	0	2	1	1	1	2	5
	20	33	35		14	7	13	3	1	12	20	26
Males												
Catatonic.....(10)	2	7	8	(8)	4	0	4	0	0	2	8	10
Paranoid.....(19)	6	9	16	(11)	7	0	3	1	0	8	3	6
Hebephrenic.....(12)	5	9	10	(7)	3	1	3	0	0	5	5	6
Simple.....(2)	0	1	0	(1)	0	0	1	0	0	1	1	1
Unclassified.....(7)	2	4	3	(2)	1	1	0	0	0	5	2	2
	15	30	37		15	2	11	1	0	21	19	25
Total.....	35	63	72		29	9	24	4	1	33	39	51

Thinking Difficulties.—Scattering, blocking or other thinking difficulties occurred in 36 per cent of the group. These difficulties included deficits of intellectual assets for the time being, among which was the inability to grasp absurdities or abstract terms or even to follow the gist of a short story. Since many of these patients represent early admissions to the clinic, they were not always given specific thinking tests, many of which were later developments at the clinic. Certain specific thinking tests, however, were performed on 50 patients. Half of the patients were not subjected to tests for the reason that they either refused or were unable to cooperate. The remaining 50 (27 men and 23 women) were given 56 tests. Eleven patients showed no defects. One of the 3 catatonic women who saw the test story had difficulty with the definitions of abstract terms. One of the 5 paranoid men who grasped the story was not able to perform the Hausmann fusion test

correctly. The hebephrenic man who saw the Binet absurdities failed, however, to see any absurdity in the Hausmann test. The paranoid women who only partly recognized absurdities in the Hausman test also failed to define abstract terms. The women with an unclassified psychosis who saw the Hausmann absurdities did poorly on the concentration test. The woman with an unclassified type of schizophrenia who had normal concentration only partly saw the Hausmann absurdities. Therefore, 11 of the 23 women tested had difficulties of thinking. Fifteen of the 27 men to whom tests were given also showed one or more defects. Unfortunately, we have no comparative material for this factor, but the finding of a thinking defect in only 36 per cent of the group seems to point to the conclusion that in the recovered patients the thinking processes are less seriously disturbed.

Delusions.—Thirteen of the 100 patients exhibited no delusional material and these were only among those with the hebephrenic and simple types. Of the other 87 patients, 74 projected their emotional material on their environment and 13 were preoccupied with autopsychic delusions. A very few entertained both types of delusions. There was no essential difference in this between the catatonic, the hebephrenic and the paranoid type. Of the 13 patients with autopsychic delusions, 11 showed predominance of affect in the psychotic picture. The delusions were predominantly self derogatory, such as ideas of being wicked, of having betrayed the family, of being the cause of war, of being dead, of the mind being gone, of having a bad effect on the family and of having ruined himself. These 11 patients were described at the time as depressed, crying, brooding or hopeless. The delusions occurred with equal frequency in all types of the parergasic reaction. One catatonic man stated that he was a woman. Others, for example, believed themselves to be the Almighty, a preacher, a person of great wealth or one with great sex power.

Delusional projections, therefore, are common and do not seem to be prognostically unfavorable.

Somatic Delusions.—Interestingly, practically none (only 5) of these patients had been concerned at the onset with bodily complaints to the point of hypochondriasis, although a few complained of headache and other pain, sweating, weakness, fatigue, palpitation, dizziness, globus, etc., while in the clinic. During the psychosis, however, about half of them exhibited actual delusions of body distortion, such as peculiar sensations in the head—of pressure, bursting, whirling, air, fire, noises, clots, moving objects, shrinking, clicking, emptiness or simply pain. These difficulties may have been felt also in other parts of the body. There were other ideas, such as those of the nose hanging loose, of the left side being different or having electricity or being "Mexican," of worms or poison penetrating the wall of the bowel, of electricity or

radium in the body or various of its parts, of the ears being pulled through the walls, of the tongue being green or of the eyes drawing. One man said that his left ear heard dirtier words than the right.

Thus, the absence of insidious hypochondriacal complaining during the onset of the illness may represent a favorable aspect, even though the tendency occurs in the psychotic process.

Negativism.—In all, 54 patients, chiefly of the catatonic group, showed negativism. This was manifested most frequently in refusal to eat. There was refusal also to speak, to enter activities, to move, to open the eyes. Attempts to feed or to move some of the patients were often met with various degrees of resistance. One catatonic patient exhibited fury not only when he was tube fed but when he saw others being nourished in the same way.

Mannerisms.—The 35 patients who were manneristic resorted to grimacing, odd postures, rhythmic movements, peculiar gait, talking with the tongue protruded, symbolic attitudes, silly smiling, somersaults, etc. They were predominantly in the catatonic group.

Panics.—Forty-four patients exhibited excitements or panics, with fright, screaming, running, assaults or attempts at suicide in a state of fear. There was no significant difference in the clinical groups.

Stupors.—Stupors occurred predominantly in the catatonic group and were accompanied by mutism, rigidity, fixed postures, retention of excreta or voiding and soiling, stereotypy and refusal of food and water. Stupor was seen in 38 patients, of whom 21 were in the catatonic group. Nine paranoid and 3 hebephrenic patients showed phases of stuporous behavior.

Passivity.—A little over one third (or 35) of the patients showed definite passivity, such as the feeling of being talked through, of the thoughts and mind being read, of being commanded to submit the will, of being under guidance, of being directed by voices to look at light, to hold saliva or to sacrifice self, of being influenced to have headache or stupor, of something being done to them. One showed automatic writing. These features of passivity occurred with about equal frequency in the catatonic and in the paranoid group of patients.

Influence.—Some of these patients and others (39 in all) had ideas of influence, such as being ordered (by the lights, God, etc.) to kill or to imitate speech and movements; of being hypnotized, of being under the control of planets, of being tested or of being experimented on. Some sent messages and received them by radio, by telegraphy, by telepathy or by the stars; some could read minds and attract women, draw boats to themselves, pull down the sun, influence others from the tub; some had special power working with them. Again, there was no difference in the clinical groups.

Insight.—Of these patients at the time of discharge, only 17 had obtained what was considered to be adequate insight, although 44 others appeared to have partial insight. Probably more than this number had a better understanding of their illness than they cared to admit. Some of the patients refused or were upset by attempts to discuss the underlying factors. Some acquired good insight between periods of delusions. The poorest insight was obtained in the paranoid group. Since we are dealing only with recovered patients, the presence of insight at the time of discharge is presumably not highly important for recovery.

TABLE 9.—*Distribution of Thinking Disorders, Delusions, Insight, etc.*

Type of Schizophrenia	Disorders of Thinking	Delusions										Insight		
		Allopsychic	Autopsychic	None	Hypochondriasis or Somatic Delusions	Negativism	Mannerisms	Excitement Pains	Stupors	Passivity	Influence	Obtained	Not Obtained	Questionable or Partial
Females														
Catatonic....(14)	3	13	1	0	8	11	10	8	13	6	4	4	8	2
Paranoid....(17)	6	16	1	0	6	10	6	10	6	9	11	1	14	2
Hebephrenic..(9)	3	5	1	3	6	4	3	2	0	3	1	2	4	3
Simple.....(1)	0	..	..	1	1	1	0	0	..	0	0	..	1	..
Unclassified...(9)	4	5	..	4	5	6	2	5	2	1	5	2	3	4
	16	39	3	8	26	32	21	25	21	19	20	9	30	11
Males														
Catatonic....(10)	4	7	3	0	6	7	5	5	8	6	6	1	5	4
Paranoid....(19)	8	17	2	0	8	9	1	6	3	8	9	3	10	6
Hebephrenic.(12)	4	9	2	1	5	3	6	4	3	1	4	1	11	0
Simple.....(2)	1	..	..	2	2	1	0	1	0	0	0	1	1	0
Unclassified...(7)	3	2	3	2	4	2	2	3	3	1	0	2	2	3
	20	35	10	5	25	22	14	19	17	16	19	8	29	13
Both.....	36	74	13	13	51	54	35	44	38	35	39	17	59	24

Table 9 shows the distribution of thinking disorders; delusions, hypochondriasis or somatic delusions; negativisms; mannerisms; panics; stupors; passivity; influence, and insight.

Scrutiny of table 9 allows certain conclusions. Relatively intact thinking is maintained; hypochondriacal concern during onset is uncommon; the presence of negativism, mannerisms, panic, stupor and features of passivity is not necessarily ominous, nor is the presence of insight characteristic of this group of recovered patients.

Life Experiences.—One of our major interests was to see whether or not the psychotic attack seemed to derive understandably from the factors in the previous life or from specific modes of reacting. In 56 of the patients, it was clear that the dynamics of the illness had origin in actual life experiences. In the remaining 44, the illness seemed more abrupt in appearance and foreign to the previous mode of reaction of the

personality. The following case will show how the material of the personality clearly emerges in the psychotic picture. In this case, the psychosis appeared as an autistic and uncritical solution of the patient's personal life, in which sexuality was blended with religion to produce an immaculate conception.

An unmarried woman aged 29, a clerk, the daughter of a stone cutter, who had been ambitious for education which she was never financially able to have, entered the hospital on June 1, 1927. For three years she had been unable to work. She expressed loss of confidence, complained of multiple discomforts in her head and eyes, stated that she was fatigued, depressed, stupid and irritated to the point of tantrums by slight noises and was convinced that she was misunderstood by her family and that people were against her.

Since the age of 23 she had felt less capable at work, had lost confidence in her ability, was easily upset and felt herself less clever than other people. For six months prior to admission she had sat around home "resting her nerves" and complaining of her physical status. She entered the hospital willingly, spoke of a depressed mood, which was worse in the morning, showed some insight into her difficulties and had well preserved intellectual resources. In the hospital she became progressively more preoccupied and daydreaming. Thinking became more and more fanciful. She spoke a great deal of being stupid and of people thinking she was stupid. Conversation slowly became more incoherent. Her words showed marked variations, from weeping to smiling; she began to speak of hearing God's voice telling her that she must reveal everything to the physician, that she had lived a wicked life and was endeavoring to follow the straight and narrow path. She saw the naked body of Christ on the Cross, acquired the idea that she was to be Christ's wife and became convinced that the physician was Christ. Within six weeks she was convinced that she was to have a child whose father would be either the physician or God, that the child would be Christ, that it would be born without passion, would be good and pure and would be born by a miraculous impregnation. Ideas of purity became prominent; she feared touching her vulva and tried to prevent her clothes from touching her. She became increasingly careless in appearance and childish in behavior and showed a great deal of foolish giggling; she had religious ideas and became convinced that she knew more men than any girl in the world; she believed that she could tell what people were to say before they spoke. Because of the progressive autistic development, she was transferred to a state hospital, where, after five months, the delusions disappeared. The patient was discharged at the end of six months and has remained at home since 1929. She is considered well by herself and by her family, is interested in the home, is industrious and energetic and has many friends.

The physical examination was noncontributory. She was of squat, obese build.

The family history was outstanding. The paternal grandfather had a mental illness; the maternal grandfather was alcoholic. The maternal grandmother and the maternal aunt had been hospitalized for depressions, from which they recovered. Two paternal uncles were in mental disease hospitals.

The patient's birth and early development were normal except that she did not speak clearly until the age of 7. She left school in the eighth grade, at the age of 14; she never got on well with other girls, being always easily offended. She longed to become a teacher, but felt she had to sacrifice her ambition to earn money for the family. She remained nine years as a clerk in a wholesale grocery, prior to giving up her work, at the age of 26. She had always been overly sensitive, holding grudges against people for long periods, was nonconfiding, critical,

suspicious that people were against her and jealous of her father's favoritism toward a younger sister. Her only love affair was with a wealthy man; it lasted four years and was terminated by him.

Thus, we have the case of a spoiled oldest daughter of a family of 5, who was jealous and resentful of her father's favoritism toward a younger sister, had in childhood many thoughts of the death of her sister, was disappointed in her only love affair, at the age of 23, and was thwarted in her ambition to become a teacher, handicapped in her general social adaptation and overconscientious and overstriving in her makeup. She became more and more convinced of her own stupidity, finally giving up her work at the age of 26; she acquired insistent physical complaints, gave way to a phase of autistic and hallucinated conviction of communication with God and of immaculate conception by her physician and became progressively more

TABLE 10.—*Factors Contributing to Recovery and Its Maintenance*

Type of Schizophrenia	Favorable Environment (Cooperative Family)	Followed After Discharge: Clinic, Physician or Social Service	Patient's Use of Clinic Advice	Causal Strain Removed	Satisfactory Work	Factors Unknown	Observation and Satisfactory Work	Favorable Environment and Work	Use of Advice and Satisfactory Work	Strain Removed and Satisfactory Work	Favorable Environment, Observation and Satisfactory Work
Females											
Catatonic.....(14)	3	5	2	1	0	1	1	0	0	0	0
Paranoid.....(17)	0	6	1	2	3	5	0	0	0	0	0
Hebephrenic.....(9)	3	3	0	1	1	1	0	0	0	0	0
Simple.....(1)	0	1	0	0	0	0	0	0	0	0	0
Unclassified.....(9)	0	3	1	0	0	5	0	0	0	0	0
	6	18	4	4	4	12	1	0	0	0	0
Males											
Catatonic.....(10)	4	2	1	0	0	2	0	0	0	1	0
Paranoid.....(19)	3	3	1	7	0	2	0	1	1	1	0
Hebephrenic.....(12)	3	3	0	2	1	2	1	0	0	0	0
Simple.....(2)	1	0	1	0	0	0	0	0	0	0	0
Unclassified.....(7)	0	5	0	1	0	0	0	0	0	0	1
	11	13	3	10	1	6	1	1	1	2	1
Both.....	17	31	7	14	5	18	2	1	1	2	1

childish in behavior and scattered in conversation during two months in the hospital. Six months later she was discharged from a state hospital as recovered and has remained well in a relatively sheltered environment throughout the subsequent thirteen years.

Factors in Recovery.—These are not always easy to evaluate. From a careful scrutiny of the records, certain specific factors stand out frequently enough to be worthy of consideration. In 82 per cent of the cases, it is possible to see that recovery and its maintenance were dependent on certain specific items. These are enumerated in table 10.

In attributing recovery in these cases to any specific factor, one is faced with the fact that there have been cases of nonrecovery in which the factors on the surface did not appear very different. In the cases of recovery, however, one is sometimes able to get a logical statement

from the patient concerning what helped him most. Often he attributes his recovery to the help of the clinic. This is likely not mere tactfulness, since the patient often writes to ask for advice and to report spontaneously his progress with the help of the advice and since a considerable number of patients return to the clinic on their own initiative. In 34 per cent of the cases of recovery, contact with the clinic physician or social agencies seemed to be the chief aid to recovery. In 19 per cent a favorable environment with a cooperative family existed.

In some of the cases in which the difficulty arose while the patient was attempting an achievement beyond him, the advice of the clinic has been followed regarding the seeking of a simpler activity, with only cautious adding to its complexity and scope. When there was a striking conflict between a desired profession and one in which money could be made immediately, or when the patient was thwarted in entering the hoped-for activity for other reasons, the help of the clinic in bringing the patient to a satisfying decision or in adjusting the environmental factors to enable him to follow his bent has stood out as an aid to recovery.

In the case of patients approximately between the ages of 16 and 20, there are sex difficulties which can be ventilated and explained, the patient being thus given workable insight on which to base his posthospital living.

A comparison of sex difficulties in 2 sensitive women in the mid-thirties, both of whom ventilated well and achieved good insight, is interesting. One of them, who was recently widowed, had a normal background; she was dependent, religious and prudish, and came for treatment after "spiritually induced" orgasms. The other, single and a teacher, whose grandmother had been psychotic, was interested in psychology and fell in love with a psychoanalyst. Each patient came to recognize her disguised eroticism, cooperated with clinic advice and returned to active and constructive living. The widow met future strains with recall of clinic suggestions, but with strong religious coloring. The teacher went into another line of work, as suggested, and consulted a woman analyst on occasions of strain. A third woman, aged 31, with a background of depression was able to recognize the dangers in her fantasy living which had brought her to a painful autistic love affair. She returned to her restricted life and adjusted, with no religious or psychologic reasoning, to an unselfish and helpful life. One patient spent three years (from the ages of 32 to 35) continuously in hospitals, in a much disturbed state, after a sex upheaval. She kept in close touch with the hospital, especially with one physician, and had no relapses during the ensuing sixteen years. She was successful in her teaching career and had an adequate social life.

There are cases in which a strain within the home can be removed by discussion with the psychiatrist of matters that could be ventilated in no other way. Contraceptive worries, financial strains and difficulties with relatives have been faced frankly by the patient and the family with the physician's help and the best method worked out for either removing the difficulties or adjusting to them.

One of our patients, who came from an unsympathetic home in which he appeared to be discriminated against and the onset of whose illness

TABLE 11.—*Data on Relation of Psychosis to Life Experiences, Duration of Recovery and Prognosis on Discharge*

Type of Schizophrenia	Is Psychosis Understandable in Terms of Life Problem and Modes of Reacting?		Duration of Recovery				Prognosis on Discharge				
	Yes	No	5-10 Years	11-15 Years	16-20 Years	21-25 Years	For Recovery	For Recurrence	Unfavorable	Questionable	Not Stated
Females											
Catatonic.....(14)	10	4	6	4	4	..	1	1	4	4	4
Paranoid.....(17)	5	12	8	3	5	1	0	3	3	4	7
Hebephrenic.....(9)	5	4	5	3	1	..	1	..	2	3	3
Simple.....(1)	..	1	..	..	..	1	..	..	..	..	1
Unclassified.....(9)	6	3	3	2	3	1	..	2	3	2	2
	26	24	22	12	13	3	2	6	12	13	17
Males											
Catatonic.....(10)	6	4	4	6	..	..	..	..	5	1	4
Paraniod.....(19)	13	6	8	8	3	..	2	..	5	4	8
Hebephrenic.....(12)	8	4	6	4	2	..	1	2	4	2	3
Simple.....(2)	1	1	..	..	2	..	1	..	1	..	..
Unclassified.....(7)	2	5	5	1	1	..	..	..	2	2	3
	30	20	23	19	8	0	4	2	17	9	18
Male and female.....	56	44	45	31	21	3	6	8	29	22	35
Number of female patients admitted during same half-decade.....			13	22	11	4					
Number of male patients admitted during same half-decade.....			10	14	18	8					
Total number admitted each previous half-decade.....			23	36	29	12					

followed a jilting, recovered after three months' treatment in the clinic and one year later made a happy marriage. There have been no upsets in the twelve years since his discharge. One effeminate patient who had been jilted entered a homosexual panic. He married within a year after discharge and never had a relapse.

The influence of a sympathetic environment can be found in cases in which the patient has returned to an understanding employer who appreciated his good workmanship. One has been fortunate enough to work under a headmaster who recognizes his success and good influence over his pupils, although he easily becomes difficult outside of the classroom. One patient, a salesman, withdrew from obvious supervision of

his family, recovered by living alone near a golf course and gradually emerged into successful salesmanship. Another adjusted under army life.

Two patients who appeared to need further hospitalization were taken to the country by relatives who devoted their entire time to their care for many months. In the case of 1 of these patients, the mother, a physician, had felt unable to give time to his upbringing. However, after his sexual upheaval, with marked erotic-religious content, she devoted her best efforts to his adjustment, guiding him through school into professional training. He emerged well.

It will be seen that by far the most striking factor seems to be the contact which is maintained with the clinic throughout subsequent years, usually with a physician on the staff, sometimes with the social worker. Thirty-one of the recovered patients were followed for a time after discharge.

Duration of Recovery.—All the patients have maintained recovery for at least five years. In table 11 the figures for duration of recovery are summarized, and it will be seen that of 12 patients admitted twenty-five years ago, only 3 have remained consistently well during the entire interval. For the twenty year span, 21 of 29 patients have remained well throughout. All of the 23 patients admitted five to ten years ago have remained well throughout that interval. There is some indication, however, that a follow-up period of five, or even ten, years is likely to show a better course than scrutiny of a longer interval, such as fifteen to twenty-five years. Nonetheless, although there have been ups and downs in the progress of these persons, they were all able finally to effect a satisfactory recovery.

Prognosis.—Prognosis in cases of schizophrenia is notoriously difficult. At the time of discharge, 13 patients were considered recovered or well, and 77 others showed various stages of improvement, outlined in table 12.

More than striking is the reluctance that physicians show in considering the possibility of future recovery for the schizophrenic patient. This is undoubtedly in part a hang-over from the kraepelinian emphasis on deterioration as a major criterion of the disturbance. It is due also in part to the fact that recovery at the time of discharge is often not complete. Also, for too long has the plasticity that may be present in the patient not been recognized and the factor of constructive growth in subsequent years not been allowed for.

At the time of discharge from this hospital few of these 100 patients seemed completely recovered. Thirty-seven of them had showed no improvement in their condition, and 24 had been transferred to other hos-

pitals for continued care. This experience should lead one to even greater hesitancy in pronouncing a necessarily poor outcome for the schizophrenic illness.

In 65 cases a prognosis had been made by the attending physician. In only 6 of these was the opportunity for complete recovery considered. In 8 cases it was thought that recurrence was likely. In 29 cases the prognosis was unfavorable and in 22 questionable.

The unfavorable prognosis was frequently predicted on the basis of the elements that established the diagnosis. Some of the reasons given for pessimism were: presence of somatopsychic reference; lowering of standard of cleanliness for several years; poor contact; lack of affect; acceptance of delusions; residue of sensitive points; failure to achieve

TABLE 12.—*Condition on Discharge from Henry Phipps Psychiatric Clinic*

Type of Schizophrenia	Improved		Unimproved		Recovered
	Number	No. of These Transferred to Hospitals	Number	No. of These Transferred to Hospitals	
Females					
Catatonic.....(14)	6	1	3	1	5
Paranoid.....(17)	5	1	10	1	2
Hebephrenic.....(9)	6	0	2	1	1
Simple.....(1)	1	1	..	..	..
Unclassified.....(9)	4	0	3	3	2
	22		18		10
Males					
Catatonic.....(10)	8	0	2	2	0
Paranoid.....(19)	10	2	7	5	2
Hebephrenic.....(12)	5	0	6	2	1
Simple.....(2)	1	0	1	1	0
Unclassified.....(7)	4	0	3	3	0
	28		19		3

insight; presence of empty talk; grimacing; duration of illness; unfavorable personality; fixity of delusions; poverty of resources; long prodromal uneasiness; incongruity of thinking; presence of disorganization; living in a fantasy world without disintegration; forced activity, passivity, etc.

In spite of these features, however, the patients recovered. The kraepelinian importance of prognosis would seem to have been given a false emphasis, since in this series prognosis is seen to be uncertain and since it may do a grave injustice to the patient.

Fifteen patients, 9 of them men, left the hospital against advice. Of these, 4, all men, took up jobs almost immediately and were able to maintain their recovery. A young man with catatonia returned to his parents and was cared for by his mother, a physician, while going to school. A paranoid patient went back to college, working his way until he received his degree. A third patient, with paranoia, eloped from another hospital and was permitted by his family to live alone in the

country, where he gradually widened his contacts and ultimately returned to salesmanship. The fourth, with a hebephrenic type of the disease, who was much improved but still scattered and silly, was taken back on his job by an understanding employer. He was followed for some time by the hospital and ultimately recovered. The 1 woman patient with catatonia recovered at home, where she was able to carry out the advice given her by the hospital. The others were longer in recovering; it is striking, however, that discharge against advice may actually represent a favorable move, since it may be followed by the assumption of personal responsibility for recovery.

Summary.—Thus it appears that attempts at prognosis are likely to be misleading and that recovery may occur after dismissal from the hospital. Many factors play a role in recovery, the most striking of which are long term contact with a physician, the presence of a favorable environment and a cooperative family to which the patient is returned, removal of the precipitating strains and capacity to utilize the advice for resynthesis of the personality.

COMMENT

Prognosis for schizophrenia is fraught with difficulties, and the usual attempts are likely to be misleading. Long term contact with schizophrenic patients reveals unexpected and unpredictable changes in course and recovery. Prognoses made in the cases under discussion went considerably amiss because of neglect of any specifically available items for the determination of outcome. It would appear that the clinical picture is not a valid criterion, since such patients often show the disturbances in content of delusional ideas, hallucinations, motor overactivity and oddities and states of puzzle and panic which are commonly seen in all parergasic patients. Many factors play a role in recovery, some of which are largely unpredictable. It becomes imperative, therefore, to search for the available assets in every case, as well as to evaluate the severity or the characteristic features of the psychosis itself. Aside from the psychotic picture, one must bear in mind the complexity of components presented by the patient and the nature of the environment to which the patient returns.

From a review of the cases of these 100 recovered patients, certain conclusions are possible. The outcome would seem to be slightly better for women than for men. The hereditary factor is outstanding, a larger number having a family history of schizophrenic and affective psychoses. This would seem to mean that these patients are more susceptible to the development of schizophrenia, which of itself is of less significance than a comparable development in a better organized personality. These patients show a more characteristic schizoid personality makeup. Dis-

turbing environmental factors are prominent, and acute disrupting precipitating events are common. The role of innate intelligence and education does not seem significant.

The most favorable age of onset appears to be between 21 and 30. Thirty-four per cent of the persons in this age group had shown previous disturbances. Acute onset is the rule, and a short period of hospitalization is characteristic. Rapid recovery within six months seems to characterize the patients who have remained well. Recurrences are rare, and in no case did more than two relapses occur.

The psychosis itself commonly occurs in the presence of somatic disturbances. The affect is for the most part well preserved throughout the psychotic picture. A third of all the patients showed no hallucinations. The hallucinatory occurrence is predominant in the auditory field. Half the patients showed the capacity for establishing contact and maintaining rapport at some time during their illness. States of panic and fright are common. The thinking abilities are relatively intact. The presence of actual delusional content does not seem ominous. It is usually allopsychic in projection, but was predominantly autopsychic in 13 of the patients. Delusional hypochondriacal ideas occurred frequently, but, interestingly, hypochondriacal concern prior to the psychotic episode was relatively rare. Insight is more commonly absent, and its preservation does not seem important as a criterion for recovery. Recovery may occur after discharge from the hospital.

The most striking single factor for recovery seems to be a long term contact with a physician or a clinic. These patients are capable of accepting guidance and of resolving personal conflicts with the help of the psychiatrist. Important, also, are the presence of a favorable and understanding environment to which the patient can be returned and the help to be obtained from cooperative families in carrying out recommendations. Removal of the precipitating strains is important, as is the person's own ability to utilize advice for resynthesis of the personality.

FIBER CONNECTIONS OF CORPUS STRIATUM AS SEEN IN MARCHI PREPARATIONS

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In this investigation isolated lesions have been made in various parts of the corpus striatum with the Horsley-Clarke apparatus and the resulting degenerations analyzed through the study of Marchi preparations. The results which have been obtained correct certain misapprehensions and clarify some ambiguities regarding the myelinated efferent fibers of the globus pallidus, and certain new details regarding them have been established.

Aside from the very important work done by Wilson,[1] this method has apparently not previously been used in the study of the corpus striatum. Most of the fiber connections in this region are too complicated to be followed in sections of normal brains stained by the Weigert method or other similar technics. Some studies have been made on human brains with long-standing lesions of the cortex, basal ganglia or tegmentum, in an attempt to determine, by the resulting atrophy of other parts, the connections which exist between the several basal ganglia and between them and the cortex and tegmentum. The long papers by Kodama [2] illustrate well the futility of this method. Marchi preparations of human brains are not likely to yield much reliable information because the lesions are too diffuse and the time elapsing before death is usually long enough to allow retrograde degeneration to occur, making it impos-

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From the Institute of Neurology, Northwestern University Medical School.

The Hughlings Jackson Lecture delivered Jan. 29, 1941 at the Montreal Neurological Institute by the senior author presented the essential results of this and some other related investigations, under the title "Some Experimental Studies on the Corpus Striatum."

1. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427-492, 1914.

2. Kodama, S.: Ueber die sogenannten Basalganglien. (Morphogenetische und pathologisch-anatomische Untersuchungen), Schweiz. Arch. f. Neurol. u. Psychiat. **18**:179-246, 1926; **19**:152-176, 1926; **20**:209-261, 1927; **23**:38-100 and 179-265, 1929.

sible to determine the direction in which the fibers are running (von Economo [3]).

The literature on the fiber connections of the corpus striatum is voluminous and full of contradictions and misinformation. It would not be profitable to review it in detail. Some of the more important work will be considered and correlated with our own results in the discussion.

METHOD

Lesions were placed by Dr. Charles Berry in various parts of the corpus striatum in monkeys (Macaca mulatta) weighing between 6 and 7 pounds (2.7 and 3.2 Kg.). The lesions were made with a direct current of 3 milliamperes led in through a unipolar electrode inserted with the aid of a Horsley-Clarke instrument. Large lesions were made by placing a number of such small lesions so close together that they fused into one. The animals were killed after twelve to fourteen days, and in 1 instance after nineteen days. The material was prepared by the Swank-Davenport [4] modification of the Marchi method after perfusion of the brains with 10 per cent concentration of neutral solution of formaldehyde U. S. P. Sections 40 microns thick were cut from blocks embedded in pyroxylin, and every other section was mounted serially. In some instances the alternate sections were counterstained with cresyl violet and mounted serially. This method yields sections which are nearly free from the nonspecific black granules which so often obscure the degenerated fibers when the standard Marchi method is used. Unfortunately, normal fibers, grouped in large masses, as in the optic tract, the corpus callosum and the internal capsule, are often stained by the osmic acid in the modified technic. But such staining cannot be confused with degeneration because it is diffuse, or if individual fibers can be seen in such bundles they always have a smooth contour which contrasts sharply with the fragmented condition of degenerated fibers.

RESULTS

We gave elsewhere [5] a general account of the ansa and the fasciculus lenticularis, with drawings from transverse sections through the brain of a normal monkey to illustrate the topography of the region. Drawings showing the size and location of six of the lesions in monkeys of the present series are published in another paper.[6]

We now proceed with a description of the degenerations observed in this series of monkeys. For clarity of presentation, descriptions will be made of individual brains, but each observation has been confirmed by study of other brains of the series.

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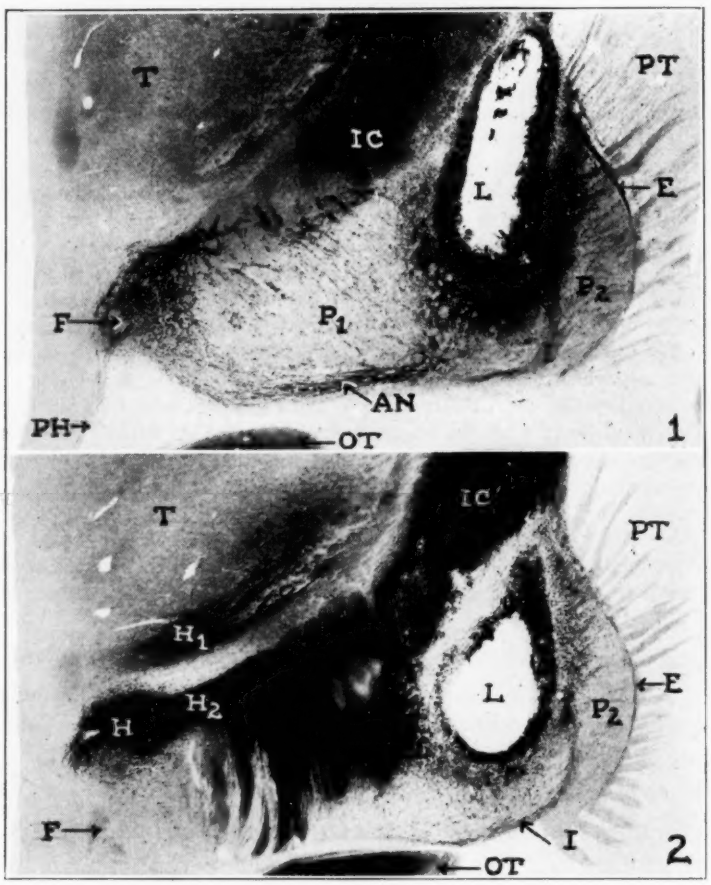
3. von Economo, C.: Wilsons Krankheit und das Syndrome du Corps strié, Zentralbl. f. d. ges. Neurol. u. Psychiat. **33**:173-209, 1918.

4. Swank, R. L., and Davenport, H. A.: Chlorate-Osmic-Formalin Method for Staining Degenerating Myelin, Stain Technol. **10**:87-90, 1935.

5. Ranson, S. W., and Ranson, M.: Pallidofugal Fibers in the Monkey, Arch. Neurol. & Psychiat. **42**:1059-1067 (Dec.) 1939.

6. Ranson, S. W., and Berry, C.: Observations on Monkeys with Bilateral Lesions of the Globus Pallidus, Arch. Neurol. & Psychiat., to be published.

The Ansa Lenticularis.—On the right side of the brain of monkey 13 a large lesion was found in the lateral part of the internal division of the globus pallidus, involving also the internal medullary lamina and the dorsomedial part of the external division (fig. 1). The lesion extended through about one half of the anteroposterior extent of the pallidum,



Figs. 1-2.—Photomicrographs from sections of the brain of monkey 13. The section in figure 2 was taken from a level behind that of figure 1.

The following abbreviations are used in these figures and in the following figures: *AC*, anterior commissure; *AD*, nucleus anterodorsalis; *AL*, nucleus anteroventralis; *AN*, ansa lenticularis; *BP*, basis pedunculi; *C*, caudate nucleus; *CC*, corpus callosum; *E*, external medullary lamina; *F*, fornix; *H*, field H of Forel; H_1, fasciculus thalamicus; H_2, fasciculus lenticularis; *Ha* lateral habenular nucleus; *I*, internal medullary lamina; *IC*, internal capsule; *L*, lesion; *M*, mamillary nuclei; *OT*, optic tract; P_1, internal division of globus pallidus; P_2 external division of globus pallidus; *PH*, pallidohypothalamic tract; *PT*, putamen; *SM*, stria medullaris; *SN*, substantia nigra; *ST*, stria terminalis; *STh*, subthalamic nucleus; *T*, thalamus, and *ZI*, zona incerta.

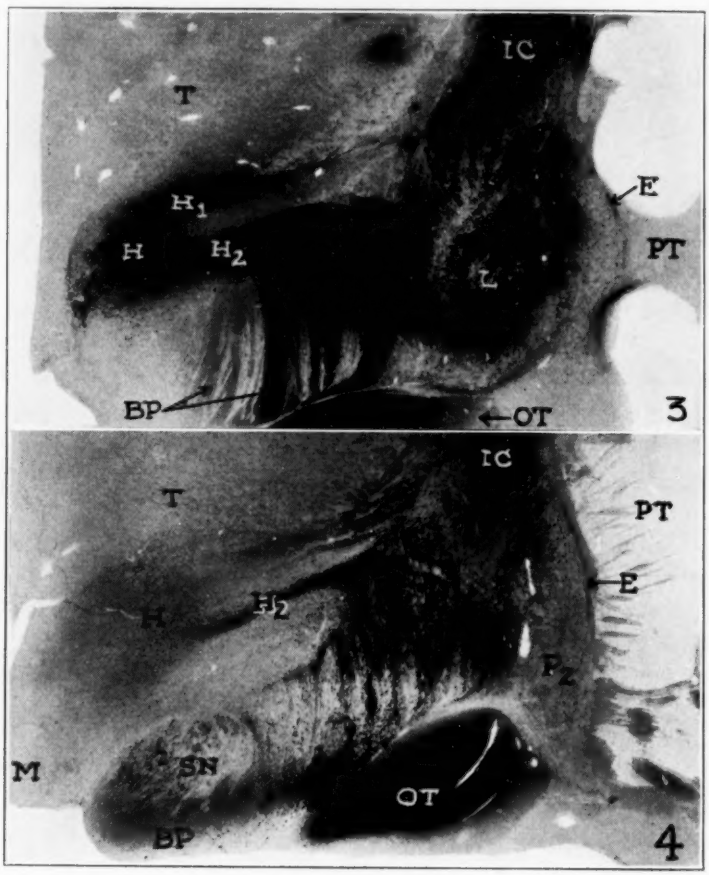
leaving its ventral fourth intact. In the photograph, degenerated fibers of large caliber run ventrally from the lesion to reach the ventral part of the internal division of the globus pallidus. They pass medially at or near the ventral surface of this nucleus and then turn dorsally around its medial border. Having reached a position between the fornix and the apex of the globus pallidus, they turn at a right angle to the plane of the section and pass caudally. They run from this point posteriorly, in the lateral part of the hypothalamus, as far as the field H of Forel (figs. 2 and 3). It is important to note that these degenerated fibers of large caliber are seen neither in the internal or external medullary lamina nor in the external division of the globus pallidus. This may be taken as evidence that the ansal fibers arise from the internal, and not from the external, division. The internal and external medullary laminas contain fine degenerated fibers, but we could find no evidence that they contributed to the formation of the ansa.

Figure 1 was taken from a section through the ansa near its posterior border. From this level forward to the anterior extremity of the internal division ansal fibers are found. The external division extends farther forward, but it contains no large fibers and no fibers can be traced from it into the ansa. Figure 6 represents a section through the most anterior part of the internal division of the globus pallidus of another monkey. The lesion was situated about 1 mm. farther back. The coarse degenerated fibers seen in the figure run forward through the internal division to emerge near the anterior end of its medial border. After emerging, these fibers turn backward to join the bundle formed by the main part of the ansa.

The Fasciculus Lenticularis.—This fasciculus, also known as the field H_2 of Forel, arises from the internal division of the globus pallidus behind the origin of the ansa, but overlapping it to some extent, as shown in figure 1. Here there may be seen fibers of large caliber running medially and dorsally through the internal division. They become assembled into bundles which enter the internal capsule and, at a slightly more posterior level, cross the capsule to its dorsomedial surface and unite to form the fasciculus lenticularis. This fasciculus is shown in figures 2 and 3, representing sections from the same brain taken at more caudal levels than that shown in figure 1. In these sections the course of the fibers through the globus pallidus and internal capsule is obscured by the lesion and by diffuse blackening of the internal capsule and the basis pedunculi, but in sections from other brains the fibers can be traced from the internal division of the globus pallidus through the internal capsule to its dorsomedial surface. After a short course along this surface, the fascicu-

lus lenticularis runs directly medialward into the subthalamus to join the fibers from the ansa and run backward with them to form the field H of Forel.

The fasciculus lenticularis has the form of a flat plate with a considerable anteroposterior extent. Its anterior part is thick (figs. 2 and 3). Its posterior part, which separates the subthalamic nucleus from the zona



Figs. 3-4.—Photomicrographs from sections of the brain of monkey 13. The section shown in *3* was taken behind the level of that shown in figure *2*, and the section shown in *4* behind the level of that shown in *3*.

incerta (fig. 4), is much thinner. At this level field H suddenly decreases in density. Figures 1 to 4 represent four sections from before backward through the same brain. Of the great numbers of degenerated fibers in the field H at levels 2 and 3, only a few are seen at level 4, and even these disappear a few sections farther back. This makes it clear that the

vast majority of the fibers of the ansa and fasciculus lenticularis are not continued backward into the mesencephalon. We shall demonstrate that most of them end in the diencephalon.

Pallidothalamic Fibers.—A large proportion of the degenerated fibers of field H turn dorsally into the fasciculus thalamicus, also known as the field H_1 of Forel (fig. 3), in which they run lateralward on the dorsal surface of the zona incerta and are distributed chiefly, perhaps entirely, to the nucleus ventralis anterior of the thalamus. Many of the fibers are directed forward as well as dorsolaterally and are seen in more anterior sections (fig. 2). The connection between the pallidothalamic fibers and the field H is not evident at these more anterior levels, but can be demonstrated by following the bundle backward through the series of sections. When the bundle is followed in the other direction from the level of figure 2, scattered degenerated pallidothalamic fibers can be seen still farther forward in the nucleus ventralis anterior.

Pallidohypothalamic Fibers.—These fibers form a bundle which branches off from the ansa (fig. 1) and the anterior end of the fasciculus lenticularis. Some of the fibers pass directly through the fornix; others run around it. The bundle is directed ventromedially into the hypothalamus. The more anterior fibers of the bundle mingle with undegenerated fibers from the commissure of Ganser. In 1 brain of this series it was possible to trace a degenerated fiber almost to the point of crossing. It is possible that a few fibers of pallidal origin may cross in the commissure, but it is certain that they form no more than a small minority of its fibers. The majority of the pallidohypothalamic fibers run into the hypothalamus behind the commissure of Ganser and end in the ventromedial hypothalamic nucleus. It was possible to see this termination clearly in Marchi preparations counterstained with cresyl violet.

Mesencephalic Connections.—It is generally believed that the fibers coming from the pallidum through the ansa and fasciculus lenticularis descend through field H to the red nucleus and other mesencephalic structures. But our Marchi preparations demonstrate that if any fibers take this course they are very few. Some of the fibers may end in the field H. In figure 4 this field contains scattered degenerated fibers which might be interpreted either as terminations or as fibers passing from the fasciculus lenticularis into the fasciculus thalamicus.

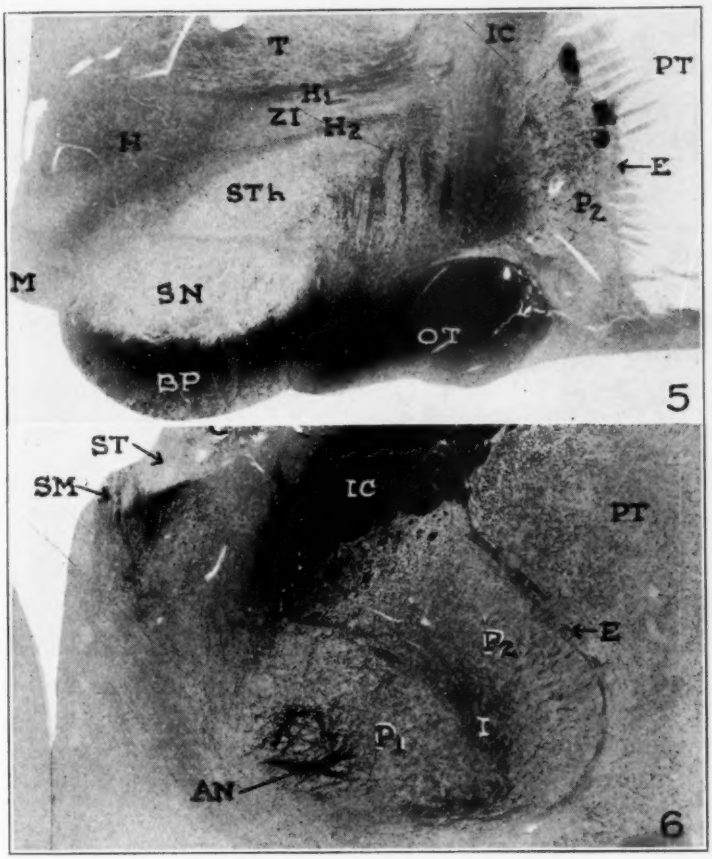
From the posterior border of the fasciculus lenticularis we have been able to trace a small number of fibers to the ventrolateral part of the capsule of the red nucleus. These ran medialward and only slightly caudalward and could scarcely be said to have descended through field H. Although the posterior part of the fasciculus lenticularis forms the dorsal capsule of the subthalamic nucleus (fig. 4), we have not been able to satisfy ourselves that it sends any pallidofugal fibers into this nucleus.

No fibers could be seen turning ventrally from it into the nucleus, except into its dorsolateral angle. This angle of the nucleus contained a few fibers which ran dorsally and medially into the fasciculus. They appeared to be fibers which, after piercing the internal capsule, traversed the dorsolateral angle of the subthalamic nucleus to reach the fasciculus. Aside from these, there were very few degenerated fibers in the nucleus immediately ventral to the fasciculus. The vast majority of the degenerated fibers entered the nucleus from its ventrolateral surface. It was likewise impossible to trace fibers from the ansa and fasciculus lenticularis through the field H into the substantia nigra, and no fibers could be traced to this destination from the posterior border of the fasciculus lenticularis.

Pallidosubthalamic Fibers.—In monkey 14 the lesion on the left side was confined almost exclusively to the external division of the globus pallidus. It occupied about one third of its anteroposterior extent, but involved only its ventral half, leaving the dorsal half intact. It damaged slightly the ventral part of the lateral border of the internal division. From the lesion degenerated fibers ran backward through the globus pallidus and near its posterior end turned and ran medialward through the ventral portion of the internal capsule, that is, just dorsal to the level at which the fibers from the capsule pass ventrally to overlie the optic tract and constitute the basis pedunculi (fig. 5). These fibers were smaller than those of the ansa or the fasciculus lenticularis. They formed bands of fibers which ran medialward through the internal capsule at right angles to the bundles of fibers of cortical origin, interlacing with these bundles like the strands of a fiber basket. In the photomicrograph one sees these bands cut across, so that the individual fibers appear as dots or short dashes. These degenerated fibers can be traced to the ventrolateral surface of the subthalamic nucleus, into which they run and in which they end. A few fine fibers of the same type can be seen over the dorsolateral angle of the subthalamic nucleus, where they lie in the posterior part of the fasciculus lenticularis. Although there is thus slight overlapping of the pallidosubthalamic fibers into the posterior border of the fasciculus lenticularis, the fibers of the two systems differ in size.

It is important to note that these pallidosubthalamic fibers are the only ones that can be traced from the lesion in the external division of the globus pallidus to a point outside of the corpus striatum, but in this preparation there are a few degenerated fibers of the ansa which can be traced from the point at which the lesion damages the ventrolateral border of the internal division. When, as in monkey 7, the lesion caused material damage to both the internal and the external division, marked degeneration of coarse fibers in the ansa and fasciculus lenticularis and of fine fibers in the pallidosubthalamic bundles resulted.

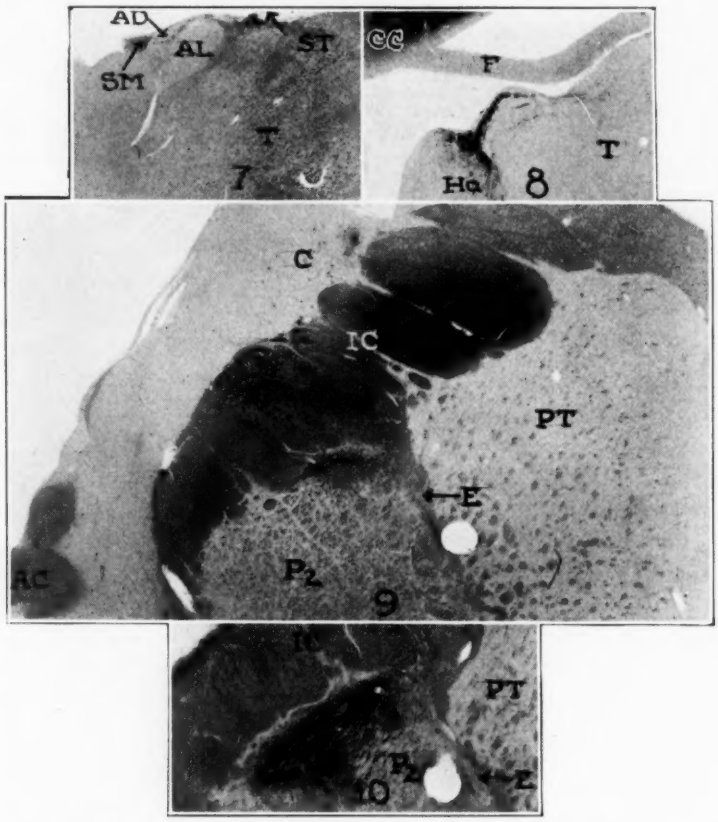
Habenular Fibers.—Fibers which end in the habenula could be followed along a circuitous course from the lesions in the globus pallidus. These are illustrated by three photomicrographs taken from sections of the brain of monkey 12 (figs. 6, 7 and 8). Degenerated fibers of about the same caliber as those going to the subthalamic nucleus can be followed dorsally from the anterior part of the globus pallidus into the stria



Figs. 5-6.—*5*, Photomicrograph from a section of the brain of monkey 14, and *6*, photomicrograph from a section of the brain of monkey 12.

medullaris and into the stratum zonale of the thalamus, immediately ventral to the stria terminalis (fig. 6). These fibers have come from a lesion in the globus pallidus situated somewhat farther back than the plane of this section. When the series is followed forward from this level, these fibers are seen to come singly or in small bundles from the globus pallidus. They cannot be followed ventrally along the course of the stria medullaris or the stria terminalis, but they can be traced backward on

the dorsal surface of the thalamus. With the appearance of the anterior thalamic nucleus, the fibers in the stria medullaris become more widely separated from those that lie ventromedial to the stria terminalis. Between these two compact groups, other fibers lie on the dorsal surface of the nucleus anteroventralis or within the substance of the nucleus anterodorsalis (fig. 7). Wilson [1] saw these fibers in that part of their course where they lie in the stratum zonale on the dorsal surface of the



Figs. 7-10.—Photomicrographs (*7*) from a section of the brain in monkey 12, behind the level of figure 6; (*8*) from a section of the brain of monkey 12, behind the level of figure 7; (*9*) from a section of the brain of monkey 16, and (*10*) from a section of the brain of monkey 16, behind the level of figure 9.

thalamus between the anterior nucleus and the tail of the caudate nucleus and described them as degenerated fibers in the "stratum subcaudatum of Sachs." As the series is followed farther backward the degenerated fibers in the anterior nucleus and those in the stratum zonale ventral to the stria terminalis run obliquely medialward through the

dorsal part of the anterior nucleus and the stratum zonale to joint the fibers in the stria medularis, with which they run to the habenula. Most of the fibers end in the lateral habenular nucleus of the same side (fig. 8), but a very few cross in the habenular commissure. There are a few fibers which fail to turn medialward from the stria terminalis, and these accompany the latter into the wall of the inferior horn of the lateral ventricle.

It seems probable that the fibers just described arise from cells in the globus pallidus. In monkey 12, from which figures 6 to 8 were taken, the lesion was in the internal division. A few of these habenular fibers were seen degenerated on the left side of the brain of monkey 14, in which the lesion was in the external division. In those cases in which the lesion involves the ventral surface of the globus pallidus or extends a slight distance beyond it there is a possibility of damage to the amygdala, but even if the degenerated fibers come from this nucleus it is clear that they must run through the globus pallidus. These habenular fibers were degenerated on both sides of the brain of monkey 13, in which there were bilateral lesions in the dorsal part of the globus pallidus. Since in this monkey the lesion did not damage the ventral third of the globus pallidus or its ventral surface on either side, it is certain that the amygdala was uninjured. It is possible that the fibers in question may only pass through the globus pallidus on their way from the amygdala, and it would be desirable to make lesions ventral to the globus pallidus to see if any degenerating fibers from such lesions would take the course of those here described.

Internal and External Medullary Laminas.—In monkey 7 the lesion on the left side involved the ventral half of the internal medullary lamina and the adjacent portions of the internal and external divisions of the globus pallidus. It caused degeneration of some fine fibers in both the internal and the external lamina. It is significant that fine degenerated fibers ran lateralward from the lesion into the external medullary lamina and then in all directions within this lamina, some of them reaching as far as its anterior, posterior and dorsal borders. It is assumed that the degenerated fibers linked the damaged area with other parts of the globus pallidus. There were degenerated fibers in the globus pallidus close to the external medullary lamina, but practically none in the putamen. This supports the generally accepted view that the latter receives no fibers from the pallidum. In preparations with lesions in the putamen, bundles of degenerated fibers were seen crossing the external medullary lamina. In doing so, they were usually deflected from their course and ran for a very short distance in this lamina before entering the external division of the globus pallidus.

The internal medullary lamina was involved in all our animals with pallidal lesions. The most instructive preparations are those from the right side of the brain of monkey 15. The lesion was confined to the internal division of the globus pallidus, except that it involved the dorsal border of the internal medullary lamina and perhaps the dorsomedial border of the external division. Many fine degenerated fibers ran lateralward from the lesion to the internal medullary lamina. Others ran obliquely forward and lateralward and entered the internal medullary lamina at levels anterior to the lesion. The fibers were distributed in all directions through the lamina. They appeared to be association fibers joining the damaged area in the internal division with other parts of the globus pallidus, and since the degeneration stopped abruptly with the internal medullary lamina and very few degenerated fibers were seen in the external division, it would appear that the fibers arose and ended within the internal division. But the possibility is not excluded that a small number of fibers from the internal division may be distributed to the external division of the globus pallidus. The lower end of the internal medullary lamina curves medially on the ventral surface of the pallidum. Fine degenerated fibers could be followed medially within it, but there was a sharp separation between these and the coarser fibers of the ansa. There was little mingling of the two kinds of fibers.

It is generally stated that fibers from the external division are distributed to the internal division of the globus pallidus. But on the left side of the brain in monkey 14, in which the anterior half of the lesion was confined to the external division, we could find no convincing evidence of such a connection between the two divisions. We do not deny that such fibers may exist, but believe that the matter deserves further study.

Fibers from the Caudate Nucleus to the Globus Pallidus.—In all 3 brains in which lesions were placed in the head of the caudate nucleus, degenerated fibers of small caliber could be traced ventralward obliquely through the internal capsule into the globus pallidus, but none of these fibers entered the putamen. For example, on the right side of the brain of monkey 16 a large lesion in the head of the caudate nucleus, which did not cause any degeneration of fibers running to the putamen or into the external medullary lamina, caused degeneration of fine fibers which could be followed obliquely through the internal capsule into the external division of the globus pallidus. In figure 9, which represents a section behind the level of the lesion, a few degenerated fibers are seen in the caudate nucleus, but most of them are crossing the internal capsule and a considerable number have reached the dorsal part of the external division of the globus pallidus, where they form a layer close to the internal capsule. There are no degenerated fibers in the external medul-

lary lamina. The number of fibers in the external division increases in the adjacent sections as the series is followed backward and as the fibers complete their crossing of the internal capsule. In figure 10 only a few degenerated fibers remain in the internal capsule; most of them have entered the external division. As the series is followed backward this bundle of degenerated fibers runs in the dorsal part of the pallidum close to the internal capsule. It gives off fibers to the external division, and, greatly reduced in size, it crosses the dorsal end of the internal medullary lamina and is lost in the internal division of the globus pallidus. Although these fibers cross this lamina, none of them run ventrally within it. All end in the pallidum; none can be traced through it into the ansa lenticularis, the fasciculus lenticularis or the strionigral bundles. It should be emphasized that our preparations from the brains of monkeys with lesions in the caudate nucleus show no degenerated fibers in the putamen or in the external and internal medullary laminas. This is surprising, for sections of normal brains stained for myelin sheaths show large numbers of fibers crossing the internal capsule from the caudate nucleus to the putamen and external medullary lamina. One might suppose, therefore, that they are ascending fibers to the caudate nucleus, but they do not degenerate into this nucleus after lesions involving the dorsal border of the external medullary lamina.

Fibers from the Putamen to the Globus Pallidus.—Lesions in the putamen caused degeneration of fine fibers which are directed medialward. These become assembled into bundles that converge in the pallidum—the "radial bundles" of Wilson. Since the putamen extends forward beyond the pallidum and the external division likewise extends forward beyond the internal division of the globus pallidus, most of these fibers are directed backward and medialward and only a few forward and medialward. In passing through the external and internal medullary laminas they are deflected slightly from their course, so that they do not appear to run directly through, but they do not run for any considerable distance in these laminas. These degenerated fibers decrease rapidly in number as they run through the pallidum, and none can be followed into the ansa and fasciculus lenticularis or the strionigral bundles. In contrast to the wealth of radial fibers seen in sections of the normal brain stained by the Weil or the Weigert method, the amount of degeneration seen in them in our Marchi preparations was surprisingly small. In the preparation illustrated by figure 1 the number of radial fibers interrupted by the lesion was enormous, but practically no evidence of their degeneration was seen in the medial part of the internal division of the globus pallidus.

Strionigral Fibers.—It has been stated that strionigral fibers arise in the caudate nucleus and putamen and run through the globus pallidus and

basis pedunculi to the substantia nigra (Riese,[7] Papez and Rundles[8]). These fibers, like the radial bundles just described, are of small caliber. They stain lightly with the Weil and Weigert methods, which may be taken to indicate that they possess a very thin myelin sheath. In sections of the normal brain of monkey and man we can easily follow them from the pallidum, where they are indistinguishable from the radial fibers, through the basis pedunculi into the substantia nigra. But in none of our Marchi preparations from the brains of monkeys with lesions in the caudate nucleus, putamen or globus pallidus have we been able to see degeneration of these fibers in the basis pedunculi. In this connection it should be noted that our preparations also fail to show degeneration in the fibers which cross the internal capsule, joining the caudate nucleus with the putamen and the external medullary lamina, and that the amount of degeneration seen in the radial fibers of the pallidum after lesions of the putamen or of the external division of the globus pallidus is small considering the great number of these fibers which have been interrupted. Since all of these fibers, like the strionigral fibers, are of small caliber and thinly myelinated, it is possible that the Marchi method as we have used it is inadequate for their demonstration.

COMMENT

Interconnections of the Pallidum and the Thalamus.—Myelinated fibers cross the internal capsule between the anterior part of the thalamus and the pallidum. They are conspicuous in frontal sections of the brain of a decorticate monkey with long-standing degeneration of the internal capsule. In these sections, stained by the Weil method, they pass from the nucleus ventralis anterior obliquely ventrally and medially across the internal capsule into the globus pallidus, chiefly into its internal division (unpublished observations). In their diagram C. and O. Vogt[9] illustrated fibers passing in both directions between the thalamus and the

7. Riese, W.: (*a*) Zur vergleichenden Anatomie der striofugalen Faserung, Anat. Anz. **57**:487-494, 1924; (*b*) Beiträge zur Faseranatomie der Stammganglien, J. f. Psychol. u. Neurol. **31**:81, 1925.

8. (*a*) Papez, J. W.: Reciprocal Connections of the Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329-349, 1938; (*b*) Thalamic Connections in a Hemidecorticate Dog, ibid. **69**:103-120, 1938. (*c*) Papez, J. W., and Rundles, R. W.: Thalamus of a Dog Without a Hemisphere Due to a Unilateral Congenital Hydrocephalus, ibid. **69**:89-102, 1938. (*d*) Rundles, R. W., and Papez, J. W.: Connections Between the Striatum and the Substantia Nigra in a Human Brain, Arch. Neurol. & Psychiat. **38**:550-563 (Sept.) 1937.

9. Vogt, C., and Vogt, O.: (*a*) Zur Kenntnis der pathologischen Veränderungen des Striatum, Heidelberg, Akad. d. Wissensch., Sitzungsb., Abt. B **14**:1-56, 1919; (*b*) Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:628-846, 1920.

globus pallidus across the internal capsule. Wilson [1] traced fibers from the medial groups of radial bundles of the globus pallidus obliquely across the basal third of the internal capsule to the lateral and ventral parts of the thalamus. These fibers degenerated after pallidal lesions but not after lesions in the putamen. Since Wilson's monkeys were allowed to live three weeks after operation, the possibility of retrograde degeneration in thalamopallidal fibers cannot be excluded. Although these fibers are regarded as pallidofugal by most authors, they did not stain by the Marchi method in any of our monkeys with pallidal lesions, and their direction must therefore be regarded as undetermined.

Pallidothalamic Fibers.—Large numbers of fibers from the globus pallidus run through the ansa and fasciculus lenticularis (field H_2) to the field H, from which they are continued through the thalamic fasciculus (field H_1) to the anterior part of the ventral thalamic nucleus. The course of these fibers has been illustrated in figures 2 and 3. Wilson [1] saw them in those of his monkeys with lesions involving the internal capsule as well as the globus pallidus; he expressed the belief that they were corticothalamic fibers running through the thalamic fasciculus. That no considerable number of the fibers of this fasciculus have a cortical origin is evidenced by the fact that they do not appear to be decreased in number in the brain of a decorticate monkey with long-standing degeneration of the internal capsule (unpublished observations).

Verhaart [10] has shown that the thalamic fasciculus is not composed of ascending fibers from the capsule of the red nucleus. The heavily myelinated field H and the equally myelinated frontal pole of the red nucleus occupy corresponding positions in sections through the respective regions, but if serial sections are followed closely there is seen to be a short distance between these two well myelinated fields in which myelinated fibers are relatively few. In sections of the brain stem of a 2 month old infant Verhaart found the field H fully myelinated, in contrast to the poorly myelinated frontal end of the capsule of the red nucleus. He clearly demonstrated that fibers of the brachium conjunctivum do not run through the field H and the thalamic fasciculus, but that they run lateralward from the upper end of the red nucleus at a slightly more posterior level.

Cecile Vogt [11] described the continuity of the lenticular and thalamic fasciculi through field H and also noted the poorly myelinated space between field H and the rostral end of the red nucleus. These observations were made on the brains of a monkey and of a newborn infant.

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10. Verhaart, W. J. C.: Comparison of the Corpus Striatum and the Red Nucleus as Subcortical Centra of the Cerebral Motor System, Psychiat. en neurol. bl. **42**:676-737, 1938.

11. Vogt, C.: La myéloarchitecture du thalamus du cercopithèque, J. f. Psychol. u. Neurol. **12**:285, 1909.

C. and O. Vogt [9] stated that thick fiber bundles from the thalamic fasciculus are distributed to the ventrolateral thalamic nucleus and that since these fibers do not pass through the thalamus into the internal capsule, they must either arise or terminate in the thalamus. From a study of horizontal sections through the brain of a newborn infant, they concluded that the fibers in question do not stand in relation to the capsule of the red nucleus, but that instead they bend in the manner of a U to pass from the thalamic fasciculus into the fasciculus lenticularis. They supported this conclusion by the statement that the thalamic fasciculus suffers proportionately when the fasciculus lenticularis is degenerated. They did not say whether the fibers in question run from the thalamus to the pallidum or in the reverse direction. They did not put this path into their now classic diagram because it had not at that time been confirmed by the Marchi method and because they felt it was possible that where the hypothesized path makes its U-shaped bend there might be located a synaptic station in field H. According to Lewy,[12] the lenticular and thalamic fasciculi contain fibers running in both directions, but the latter is mainly striopetal.

It is difficult to understand why Wilson [1] did not recognize this massive connection between the globus pallidus and the thalamus. In this connection it should be noted that the illustrations which accompany his paper are somewhat unsatisfying. About half of them are photographs of the slices of brain before they were prepared for microscopic study and show only the location of the lesions. In three illustrations the course of degenerated fibers has been indicated diagrammatically on photographs of normal brains, and the remaining figures show only short stretches of the degenerated fibers. Wilson's great contributions were the demonstration that no fibers from the putamen or the caudate nucleus run through the globus pallidus into the ansa and fasciculus lenticularis and the tracing of the course of the fibers which run from the globus pallidus to the subthalamic nucleus.

Papez and Stotler [13] expressed the belief that some of the pallidofugal fibers end in the field H and that impulses are relayed from this point to the red nucleus. According to these authors, the rest of these fibers run into the fasciculus thalamicus. The latter is, according to them, largely a recurved terminal of the lenticular fasciculus and ends in the medial border of the ventral lateral nucleus of the thalamus, more anteriorly than the radiations of the brachium conjunctivum.

The degeneration seen in our Marchi preparations furnishes a convincing demonstration of the continuity of the lenticular and the thalamic

12. Lewy, F. H.: Die Lehre vom Tonus und der Bewegung, Berlin, Julius Springer, 1923.

13. Papez, J. W., and Stotler, W. A.: Connections of the Red Nucleus, Arch. Neurol. & Psychiat. **44**:776-791 (Oct.) 1940.

fasciculus and shows that the inference of Papez and Stotler as to the direction of these fibers is correct. Our sections show, however, that the fibers terminate farther forward than these authors supposed and that most, if not all, of them end in the nucleus ventralis anterior. In the brain of the decorticate monkey already referred to, the nucleus ventralis lateralis of the thalamus was degenerated but the nucleus ventralis anterior contained normal cells, in full agreement with the work of Walker.[14] In this brain, of which alternate sections were stained by the Weil method for fibers and by the cresyl violet method for cells, it could be seen that the fibers of the fasciculus thalamicus were distributed to the region occupied by the cells of the nucleus ventralis anterior and that a prolongation of the nucleus containing normal cells extended backward along the fasciculus thalamicus into the territory of the anterior part of the nucleus ventralis lateralis. Since in this case the fibers of the fasciculus thalamicus terminated in a region of normal cells, either obviously within the nucleus ventralis anterior or in a tonguelike caudal prolongation of normal cells continuous with it, we make the statement that the fibers end in the nucleus ventralis anterior. From a study of the Marchi preparations alone, one might conclude that the fibers ended in both the nucleus ventralis anterior and the nucleus ventralis lateralis.

It is of interest that the fibers which pass obliquely through the degenerated internal capsule in the brain of the decorticate monkey connect the nucleus ventralis anterior with the pallidum, but it is not yet possible to say in which direction they run. In this connection it should be remembered that Walker [14] stated that this thalamic nucleus probably sends its fibers to the striatum rather than to the cerebral cortex.

The Pallidohypothalamic Tract.—This was not clearly distinguished from the commissure of Ganser until recently. The tract was recognized and named by Bard and Rioch [15] and described under that name by Papez,[8a] Ranson and Ranson [5] and Vidal.[16] Krieg [17] had previously described this bundle under the name "hypothalamic fasciculus" and stated that the fibers probably terminated in the ventromedial hypothalamic nucleus. In the paper by Vidal, reference is made to some of the older literature.

Pallidosubthalamic Fibers.—Fibers from the globus pallidus to the subthalamic nucleus were described by Wilson [1] as the "second division

14. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938.

15. Bard, P., and Rioch, D. McK.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73-147, 1937.

16. Vidal, F.: Pallidohypothalamic Tract or "X Bundle" of Meynert in the Rhesus Monkey, Arch. Neurol. & Psychiat. **44**:1219 (Dec.) 1940.

17. Krieg, W. J. S.: The Hypothalamus of the Albino Rat, J. Comp. Neurol. **55**:19-89, 1932.

of the ansa lenticularis." He saw that they were of smaller caliber than those of the ansa and fasciculus lenticularis proper and that they edged obliquely across the basal third of the internal capsule, crossing the capsular fasciculi as the latter extended into the basis pedunculi. According to Wilson, the great majority pass into the subthalamic nucleus, diffusing out in its interior, but some make their way to the capsule of the red nucleus and a smaller number reach the substantia nigra.

C. and O. Vogt [9] showed these pallidosubthalamic fibers clearly in a photograph of a section through the brain of a 5 month old infant, in which, owing to the unmyelinated state of the corticospinal fibers, the fibers which cross the internal capsule from the pallidum to the subthalamic nucleus stand out prominently. These authors stated that isolated destruction of the external division of the globus pallidus leads to such marked degeneration of the subthalamic nucleus that they were inclined to believe that this part of the pallidum has especially close connections with the nucleus. These authors figured the pallidosubthalamic fibers as ending in the substantia nigra, as well as the subthalamic nucleus. But in our Marchi preparations they could be traced only to the latter nucleus.

In Marchi preparations of the brain of a dog with a lesion in the caudate nucleus Grünstein [18] could trace degenerated fibers only into the globus pallidus, in which they ended. In similar preparations Riese [7b] traced degenerated fibers to the substantia nigra, but the figures which he published are not convincing. Strionigral fibers have been described by Papez and Rundles,[19] in whose papers references to the related literature will be found. These fibers are fine and thinly myelinated and stain a light and imperfect blue, thus resembling the fibers from the striatum to the pallidum. Papez expressed the belief that these fibers arise in the caudate nucleus and the putamen and run through the basis pedunculi to the substantia nigra. That there are fibers of this character connecting the corpus striatum and the substantia nigra is, we believe, beyond dispute. We have been able to identify them and trace them downward from the pallidum in sections of the normal brain of man and monkey. They can be followed more easily in the brain of a decorticate monkey with degenerated internal capsule and will be described in a subsequent publication. It was in the hope of demonstrating these fibers by the Marchi method that the present investigation was undertaken, but, to our surprise, no trace of degeneration was seen in them after lesions of the caudate nucleus, putamen or globus pallidus. The failure of these fibers to stain by the Marchi method after lesions in various parts of the corpus striatum may be due to the small amount of

18. Grünstein, A. M.: Zur Frage von den Leitungsbahnen des Corpus striatum. Vorläufige Mitteilung, Neurol. Centralbl. **30**:659, 1911.

19. Papez and Rundles.[8c] Rundles and Papez.[8d]

myelin they contain, but the possibility must not be forgotten that they may be ascending fibers from the substantia nigra.

Mesencephalic Connections.—In our preparations we were unable to trace degenerated fibers descending from the pallidum through field H to the red nucleus, the subthalamic nucleus, the substantia nigra, the nucleus of Darkshevich, the interstitial nucleus or the posterior commissure. Although C. and O. Vogt included such fibers as prominent parts of their diagram, which has subsequently been widely accepted, they were themselves clearly not too credulous, as is shown by the critical discussion which they appended to the description of this diagram.

In drawing these tracts, the Vogts were influenced by current opinion and by the observations made by von Economo [8] on the brain in a case of Wilson's disease in which a large lesion destroyed the putamen and head of the caudate nucleus and damaged, in addition, the lateral border of the globus pallidus. The extensive degenerations visualized in this case through the Marchi method could hardly all have resulted from this lesion alone; this necessitates the assumption that other parts of the brain were also involved. No satisfactory evidence was presented by von Economo that the extensive degeneration in the red nucleus, particularly in the bundles of fibers which he designated alpha and gamma, resulted from the stated lesion in the corpus striatum, since the degenerated fibers were not followed in serial section.

C. and O. Vogt [9] mentioned the bundle gamma described by von Economo as passing from the nucleus of the field of Forel to the medial part of the red nucleus and its capsule. They stated that in myelin sheath preparations of a child's brain they were able to follow the same bundle and that it passed through the red nucleus, apparently without giving off any collaterals of note, to the nucleus of Darkshevich and the posterior commissure.

They were careful to state that in the material at their disposal damage to the pallidum was always accompanied by a certain reduction in volume of the subthalamic nucleus, but never by observable change in the red nucleus or its capsule. They then pointed out that if the tracts shown in their diagram as running from the pallidum to the substantia nigra, the red nucleus and its capsule, the nucleus of Darkshevich and the interstitial nucleus really existed, the aforementioned observations would need to be explained away.

It was mentioned in a preceding paragraph that there is a poorly myelinated field intervening between field H and the upper end of the red nucleus, and we have shown that the vast majority of the fibers of the ansa and fasciculus lenticularis run to the thalamus and the hypothalamus.

Papez and Stotler,[13] knowing that few, if any, pallidofugal fibers continue through field H to the red nucleus, have suggested that some

of these fibers may terminate in synaptic relation with the cells located in this field (nucleus of Forel's field) and that through such synapses impulses may be relayed downward to the red nucleus.

If it can be shown that the strionigral fibers are indeed descending fibers, they will have to be regarded as constituting the largest, and probably the most important, path from the corpus striatum to the lower-lying brain centers. The largest unambiguously established descending path is formed by the fibers from the external division of the globus pallidus to the subthalamic nucleus. The fibers from the internal division, which run through the ansa and fasciculus lenticularis to the thalamus and hypothalamus, should probably not be listed among the descending connections.

SUMMARY

We believe that the internal division of the globus pallidus gives rise to most, if not all, of the fibers of the ansa and fasciculus lenticularis. After destruction of these bundles within the hypothalamus, the cells of the internal division disappear, while those of the external division remain normal. Lesions involving chiefly the internal division caused degeneration of the ansa and fasciculus lenticularis, while a lesion confined to the external division did not. After lesions involving both divisions, degenerating fibers could be traced into the ansa and fasciculus lenticularis from the internal division only. None of the large fibers characteristic of these fascicles could be seen in the external division or in the internal medullary lamina.

The ansa and fasciculus lenticularis unite to form a bundle which is directed caudalward in the lateral hypothalamus. From this bundle a small fascicle runs medially and ventrally into the hypothalamus. This is the pallidohypothalamic tract, and it ends in the nucleus ventromedialis. There is some intermingling of the pallidohypothalamic tract with fibers from Ganser's commissure, but we have not been able to trace any fibers from this tract across the midline.

The vast majority of the fibers of the ansa and fasciculus lenticularis run caudalward as far as the field H of Forel. They then turn dorsally and laterally in the fasciculus thalamicus to end in the nucleus ventralis anterior of the thalamus. The Vogts saw this looplike connection of the fibers of fields H_1 and H_2, but were unable to tell in which direction the fibers were running. Papez has recently recognized this loop and correctly assumed that the fibers run from the pallidum through fields H_2, H and H_1 to the thalamus. In our Marchi material this has been established beyond doubt, and it becomes clear that the number of fibers which reach the thalamus in this way is very large. Papez expressed the belief that some of the fibers end in field H, the impulses being relayed from this point to the red nucleus. We have no evidence bearing on this point. We could find no evidence in our Marchi material that

fibers from the ansa or fasciculus lenticularis descend through field H to enter the red nucleus, the subthalamic nucleus, the substantia nigra, the interstitial nucleus or the posterior commissure. Some degenerated fibers from the caudal border of the fasciculus lenticularis which did not enter field H could be traced to the ventrolateral part of the capsule of the red nucleus.

The external division of the globus pallidus gives rise to the pallidosubthalamic fibers. Arising from the cells of this division, these fibers run backward for some distance before they turn medially and cross the ventral end of the internal capsule and enter the subthalamic nucleus through its ventrolateral surface. None of these fibers could be traced to the substantia nigra or the red nucleus.

Fibers have been traced from the globus pallidus to the lateral habenular nucleus. Wilson saw these fibers in that part of their course in which they lie in the stratum zonale on the dorsum of the thalamus between the anterior nucleus and the tail of the caudate nucleus, and described them as degenerated fibers in the stratum subcaudatum.

The caudate nucleus gives rise to fibers which cross the internal capsule into the external division of the globus pallidus, within which many of them terminate. Some of them end in the internal division. But in our Marchi preparations following lesions of the caudate nucleus no degenerated fibers could be traced entirely through the globus pallidus. The putamen gives rise to fine fibers which are grouped in bundles that converge medially and enter the globus pallidus, where they end. None could be traced in our Marchi preparations through the globus pallidus. After lesions in the caudate nucleus or putamen no degenerated fibers were seen in the ansa or the fasciculus lenticularis. Nor were any pallidosubthalamic or strionigral fibers degenerated.

Strionigral fibers, joining the corpus striatum with the substantia nigra, have been described by Papez and others. They are slender and take a peculiar light bluish brown stain, so that they can be followed in sections of the normal brain stained by the Weil or the Weigert method. In our Marchi preparations we could see no evidence of their degeneration after lesions in any part of the corpus striatum. Perhaps this failure to stain was due to the small amount of myelin they contain. But one must not overlook the possibility that they may be ascending fibers from the substantia nigra to the corpus striatum.

Fiber connections between the globus pallidus and the thalamus include the numerous pallidothalamic fibers which run through fields H_2, H and H_1 to the nucleus ventralis anterior of the thalamus. In a decorticate brain, other fibers, crossing the degenerated internal capsule obliquely, were seen joining the nucleus ventralis anterior and the globus pallidus. Because none of these fibers degenerated after pallidal lesions in our monkeys, we think it probable that the direction of these fibers is from the thalamus to the pallidum.

ACUTE POSTOPERATIVE ASEPTIC LEPTOMENINGITIS

REVIEW OF CASES AND DISCUSSION OF PATHOGENESIS

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The specific form of aseptic meningitis to be presented here occasionally follows operations on the central nervous system. The condition has received little attention in surgical literature, although its syndrome must have been an occasional cause for concern to all neurosurgeons of experience. When the nature and characteristics of this inflammatory process are recognized it can be readily distinguished from bacterial meningitis.

In the syndrome of acute postoperative aseptic leptomeningitis there are recurring bouts of fever, rigidity of the neck and pleocytosis. Each reaction is of sudden, dramatic onset, but of short duration, and is preceded and followed by intervals relatively free from symptoms.

The condition is troublesome rather than dangerous, for it prolongs the convalescent period by two to six weeks, without leaving serious residual complications. It occurs most often after operations in the posterior fossa which open the cisterna magna or after supratentorial operations which have left the ventricles widely open. Prevention can depend only on an understanding of its mechanism.

We have reviewed the pertinent literature, have studied the cases which have occurred in the Royal Victoria Hospital and the Montreal Neurological Institute over a ten year period and have carried out experiments to elucidate the mechanism of postoperative aseptic meningitis. Our associate, Dr. William V. Cone, permitted us to include certain cases which occurred in his service, and Prof. E. G. D. Murray, of the department of bacteriology, made the clinical bacteriologic studies.

REPORT OF CASES

Reaction Following Simple Opening of Cavity of Previous Operative Defect.—CASE 1.—W. B., a white man aged 26, was admitted on Dec. 12, 1931 with the history of a previous left frontal craniotomy on Nov. 24, 1928. At that time a traumatic meningocerebral cicatrix involving the left frontal pole was excised in

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block. The left lateral ventricle was thus widely opened. After this operation he had remained free of seizures but was disturbed by the cosmetic effect of a defect in the skull at the operative site. He underwent a craniotomy for repair of this defect with tibial transplants on Dec. 22, 1931. At this time the dura over the cavity resulting from the previous removal was opened in order to observe what changes might have occurred. A large cavity filled with cerebrospinal fluid was found, which was lined by a smooth, shining membrane, resembling the inner surface of the dura. A small opening, the size of a little finger, at the posteroinferior angle of the cavity, was thought to communicate with the lateral ventricle, although this relationship was not demonstrated.

After operation there was definite evidence of continued leakage of blood into the subarachnoid space. The fluid was bloody for eight days and then became xanthochromic. The onset of meningitic signs and symptoms was delayed, although there was a persistent rise in temperature during the first ten postoperative days (fig. 1). On the seventeenth day there was a sudden rise of temperature, with severe headache, mental dulness and stiffness of the neck. On lumbar puncture

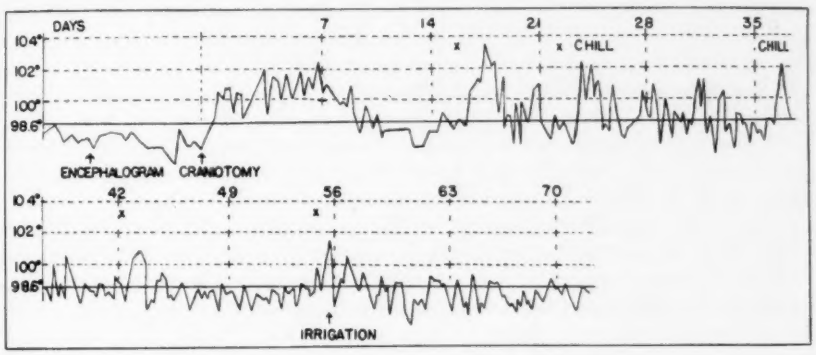

Fig. 1 (case 1).—Graphic record of temperature.

1,200 leukocytes (90 per cent polymorphonuclears) were found in each cubic millimeter of spinal fluid. Subsequently there were recurrent episodes (as illustrated in figure 1) entirely similar to the first, but ushered in by a chill on three occasions. Between each of these attacks the patient was perfectly lucid and alert mentally and was free of complaints, while with each recurrence he was dull and complained of headache and a stiff, sore neck.

The intermittent reactions subsided in about one month from the time of their onset, and the remainder of the convalescence was satisfactory except for one brief rise in temperature, which seemed to foreshadow another meningeal reaction. On this occasion craniospinal irrigation was done by passing warm Ringer's solution from a needle in the cyst formed at the site of the operative removal through the ventriculosubarachnoid pathways to a needle in the lumbar region. The temperature subsequently dropped, and symptoms were relieved.

Each of three cultures of the cerebrospinal fluid was sterile, and no evidence of extradural infection was discovered. The protein content of the spinal fluid on two occasions was found to be markedly elevated (285 and 681 mg. per hundred cubic centimeters).

In this case it was felt that the sterility of the spinal fluid was definitely established. No organisms were cultured, nor were any found

in smears. The presence of the transplanted bone was thought not to be related to the condition, since no reaction was observed at the site of the plastic repair.

In the absence of a septic cause for such meningeal incidents as occurred here, the only apparent explanation seems to be the presence of postoperative bleeding at the operative site with subsequent slow, continuous breakdown of the clot and intermittent discharge of its products into the ventriculosubarachnoid system. The surgeon expressed the opinion that no leptomeningeal reaction would have occurred had not the dura been opened.

The reactions in this case were somewhat less severe and less dramatic than those in the next case to be presented. It is important that there was correspondingly less postoperative bleeding in case 1.

Aseptic Meningitis Following Opening of Cavity of Previous Operative Defect with Further Removal of Tissue.—CASE 2.—W. O'N., a white man aged 24, was admitted on Nov. 25, 1937 with the history of a previous craniotomy on Jan. 22, 1937, at which time an arterioveneous aneurysm and cystic meningocerebral cicatrix had been removed from the left frontal lobe. Recurrence of epileptiform seizures led to a second craniotomy at the same site, on Dec. 9, 1937. The cystic cavity resulting from the previous excision was found to be smooth lined and to communicate with the left lateral ventricle. There was no evidence of recurrence of the previously removed arteriovenous aneurysm. An area of remaining scar situated posteriorly near the midline was removed. The dura was closed except for a subarachnoid drain, which was removed twenty-four hours later.

After operation there was obvious bleeding at the site of the craniotomy, for syrupy blood accumulated beneath the scalp flap, necessitating drainage by puncture on several occasions during the first week. Twice (on the fifth and sixth postoperative days) this fluid yielded micrococci on culture. During this period and for several weeks afterward red blood cells were found in the spinal fluid on lumbar puncture. The spinal fluid, at first grossly bloody, gradually became xanthochromic and remained so for an unusually long period.

Subsequently, on the twentieth postoperative day and at recurrent intervals thereafter, the course became unusually febrile. This is illustrated in figure 2. Associated with each temperature spike there were elevation of cerebrospinal fluid pressure and pleocytosis. The patient complained of chilliness or an actual chill and headache. The pulse rate was elevated with the temperature; there was stiffness of the neck, and the patient was dull, lethargic, irrational and confused. There was occasional vomiting. Repeated smears and cultures of the cerebrospinal fluid (made a total of fourteen times) proved negative for organisms. Special studies for the presence of tubercle bacilli (including animal inoculation) and for fungi also gave negative results.

Cultures of the blood were made on two occasions and were sterile. Consultation regarding the nose and throat and roentgenograms of the chest revealed nothing abnormal.

In this case, although two cultures containing micrococci were obtained from syrupy, bloody fluid accumulated beneath the scalp flap, fourteen cultures of the cerebrospinal fluid were sterile and organisms were never found in smears. The sterility of the spinal fluid would therefore seem to be reasonably well established, and the periodic

meningeal reactions must have been the result of irritation of the ventriculosubarachnoid system by some agent not bacterial.

The aseptic meningitis in this case represented, then, either a "serous" meningitis, the result of the presence adjacent to the dura of a focus of infection, or discharge into the cerebrospinal fluid breakdown products of the blood clot produced by the postoperative bleeding. That the micrococci present in the subaponeurotic hematoma were not responsible for the reactive meningitis is suggested by the absence of meningeal reaction at the time the positive cultures were obtained, by the subsidence of the reaction in the osteoplastic flap *before* the onset of the periodic meningeal irritation and by the negative results of fourteen cultures of the spinal fluid. The surgeon stated: "The fact that at the first puncture [after the onset of the reaction] the spinal fluid was a deep orange, with the white cell count 180 per cubic millimeter,

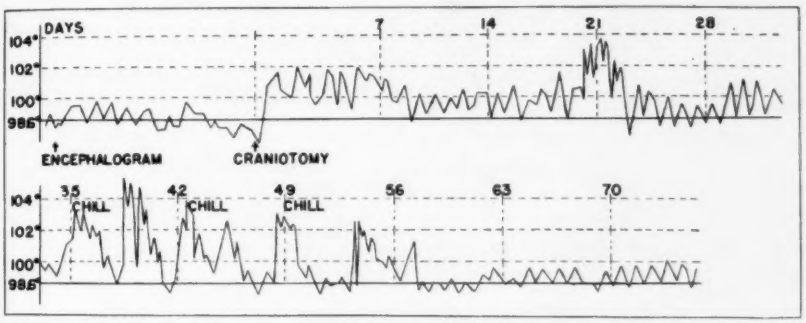

Fig. 2 (case 2).—Graphic record of temperature.

whereas it had been light in color after the original discoloration, seems to indicate that the reaction is a chemical aseptic meningitis developing from a sudden discharge into the spinal fluid of a substance which has been formed by the clot. This clot must have been sealed up so that the chemical processes could take place."

In 6 other cases similar periodic meningeal irritation resulted from the removal of a meningocerebral cicatrix. Four of these (cases 3, 4, 7 and 8, table 1) are essentially similar to the 2 cases just presented. Two of the 6 patients died, however, about sixty days after the craniotomy and excision of the cicatrix. Although the occurrence of aseptic meningitis in these 2 cases was undoubtedly contributory to the fatal outcome, in neither was it the direct cause. The autopsy observations are presented briefly, to emphasize certain points.

Reaction Following Excision of Cicatrix; Death and Autopsy.—CASE 5.—O. M., a white man aged 29, who was admitted on Feb. 28, 1935, underwent left frontal craniotomy for removal of a cicatrix involving the anterior portion of the

left and part of the right frontal lobe. The scar was removed in block, and both anterior horns were opened by the procedure.

After operation (fig. 3) he was lethargic and dull. Onset of meningeal signs occurred on the second day. Until the fifteenth day the spinal fluid contained red blood cells, in numbers decreasing from 300,000 to 3,000 per cubic millimeter. A second meningeal episode occurred on the sixteenth day and two more on the nineteenth and the twenty-second day, respectively. From then the course was progressively downhill, with increasing lack of mentation and eventual stupor. During this period the spinal fluid was never free of cells, although the count remained below 50 per cubic millimeter. Death occurred on the sixty-second postoperative day.

Autopsy revealed the immediate cause of death to be bronchopneumonia. There were diffuse ventricular enlargement and obliteration of the subarachnoid space. The cavity resulting from the operative removal communicated with both lateral ventricles (fig. 4). It measured 4 by 6 by 6 cm. Its wall was stained a deep orange-yellow, indicating the presence of blood pigment, although there

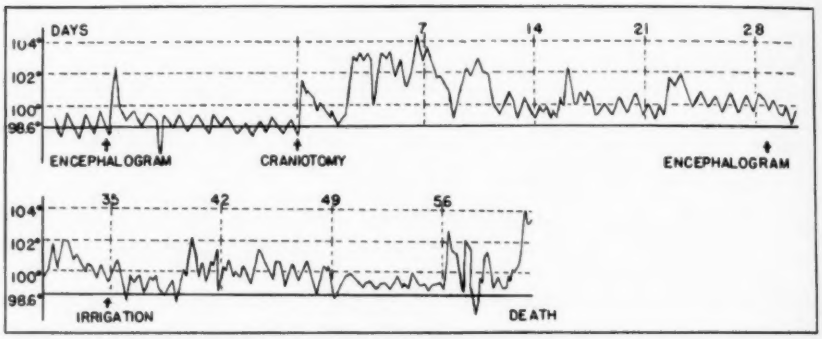

Fig. 3 (case 5).—A rather persistently maintained, low grade temperature is shown, with superimposed spikes at the times of most pronounced meningeal signs and symptoms.

was no evidence of recent bleeding. The arachnoid was generally thickened and milky, particularly at the base of the brain and over the inferior surface of the cerebellum. Some idea of the degree of inflammatory reaction may be gained from the fact that the leptomeninges ventral to the cord in the cervical region were thickened to slightly more than 1 mm. Section of the brain revealed much degenerated and sclerosed tissue in the right frontal lobe medially. Microscopic sections showed the cyst to be lined by thin membrane, beyond which a layer of albuminous material containing mononuclear cells, rod cells and compound granular corpuscles was noted. The reaction in the brain substance deep to this zone consisted of a thick layer of collagenous tissue with infiltrating lymphocytes, plasma cells and other phagocytes. Astrocytosis was observed in deeper areas. Other portions showed areas of necrosis and intense cellular reaction with phagocytic elements and collagen fiber response, as well as gliosis. No significant changes were demonstrated in the choroid plexus or in the ventricle, except for slight yellow-orange pigmentation in the choroid plexus in portion 4 of the left lateral ventricle. There was, however, definite evidence of continuing chronic inflammation in the leptomeninges, for macrophages and mononuclear cells were present in moderate numbers.

CASE 6.—H. R., a white man aged 37, who was admitted on Aug. 3, 1937, underwent craniotomy for a right frontal meningocerebral cicatrix, which proved to be cystic. The ventricle was not opened. Postoperatively (fig. 5) he dis-

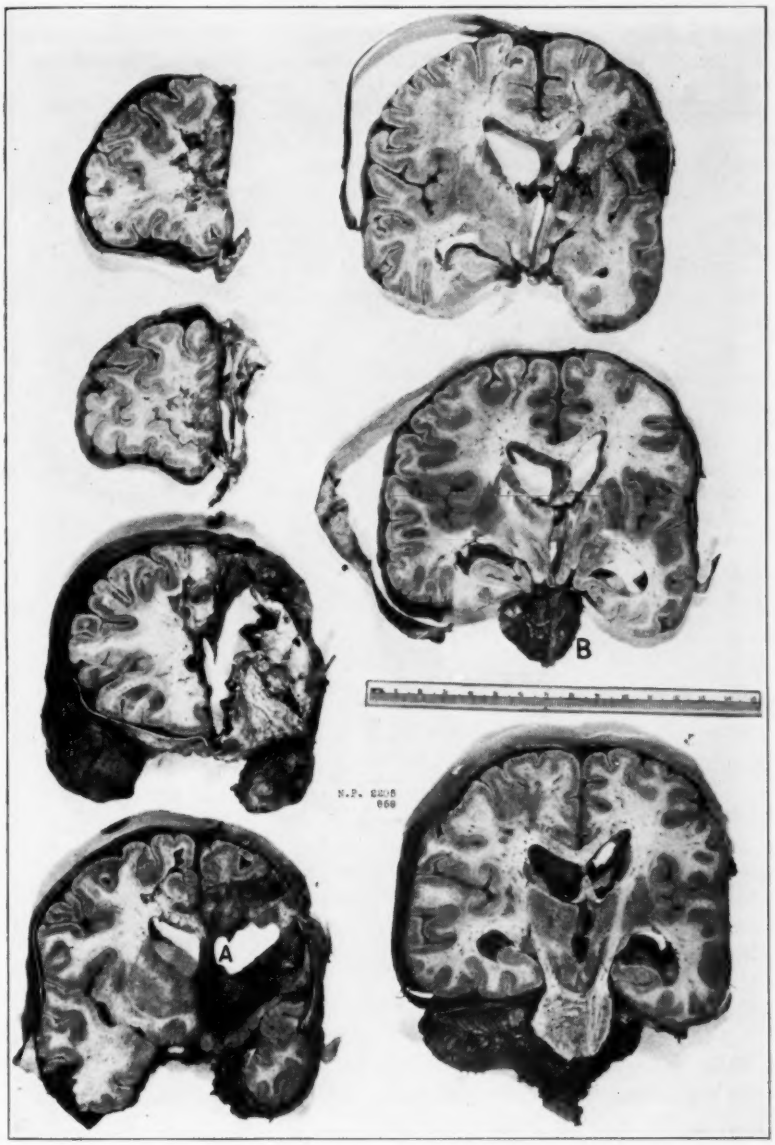

Fig. 4 (case 5).—Coronal sections of the brain showing the smoothly lined cavity at the operative site and its communication with the left lateral ventricle at the points marked by *A*. Moderate ventricular dilatation, the probable result of increasing interference with cerebrospinal fluid circulation, may be observed. Leptomeningeal thickening is apparent at *B*.

played a severe, recurrent meningeal reaction. During the first ten days there was evidence of continued slight hemorrhage at the operative site, so that reopening the flap was considered for a time. The fluid persistently contained red blood cells and remained xanthochromic for a longer period than usual. It is difficult to evade the impression that continued formation of degenerated products of blood clot, and possibly even softened brain tissue, at the site of operation was to some extent responsible for the reaction. The patient subsequently died, and autopsy showed the cause of death to have been bilateral bronchopneumonia. There was thrombophlebitis in the right femoral vein, though there was no evidence of embolism. The arachnoid was generally thickened, but was missing over the cavity resulting from the removal. The ventricles were found to be dilated slightly, and there was definite change in the brain bordering the operative defect. On section of the brain a blood clot, 1.2 to 1.5 cm. in diameter, was found between the frontal poles in the depths of the operative tract (fig. 6). It was not possible to tell grossly whether there was direct communication with the lateral ventricles. There was considerable pigmentation in the tissues in this region. Microscopic studies showed a ragged area of degeneration and infiltra-

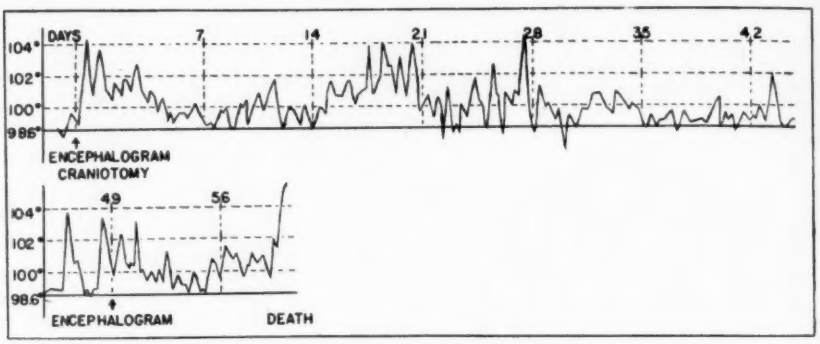

Fig. 5 (case 6).—Temperature graph.

tion in the right frontal lobe, with many mononuclear cells of all sorts. Fat-filled macrophages and compound granular corpuscles were also present in numbers in this area. Collagenous tissue showed evidence of proliferation, and astrocytosis was prominent. There was also evidence of continuing chronic inflammation in the leptomeninges at a distance from the operative site. Mononuclear cells and macrophages were observed in these tissues, although leptomeningeal fibrosis was much less marked in this case than in the preceding one (fig. 7).

The observations in both these cases are entirely compatible with the postulated explanation as set forth thus far.

In both there was evidence of blood pigmentation among the tissues at the operative site. Both operative cavities communicated with the subarachnoid and/or ventricular fluids, and thus an avenue for discharge of the contents of the operative cyst was established. The absence of inflammatory changes in the ependyma or in the choroid plexuses and the presence of continuing chronic inflammatory changes in the leptomeninges strongly indicate that the irritant substances causing the aseptic meningitis exert their most profound effect in the leptomeninges.

In 2 cases (9 and 10) the reaction followed the removal of a large supratentorial neoplasm. Again, the typical course was observed—recurring episodes of leptomeningitis with fever, stiff neck, headache and pleocytosis. In case 9 there was a postoperative subaponeurotic hematoma, just as there had been in several of the cases of cicatrix.

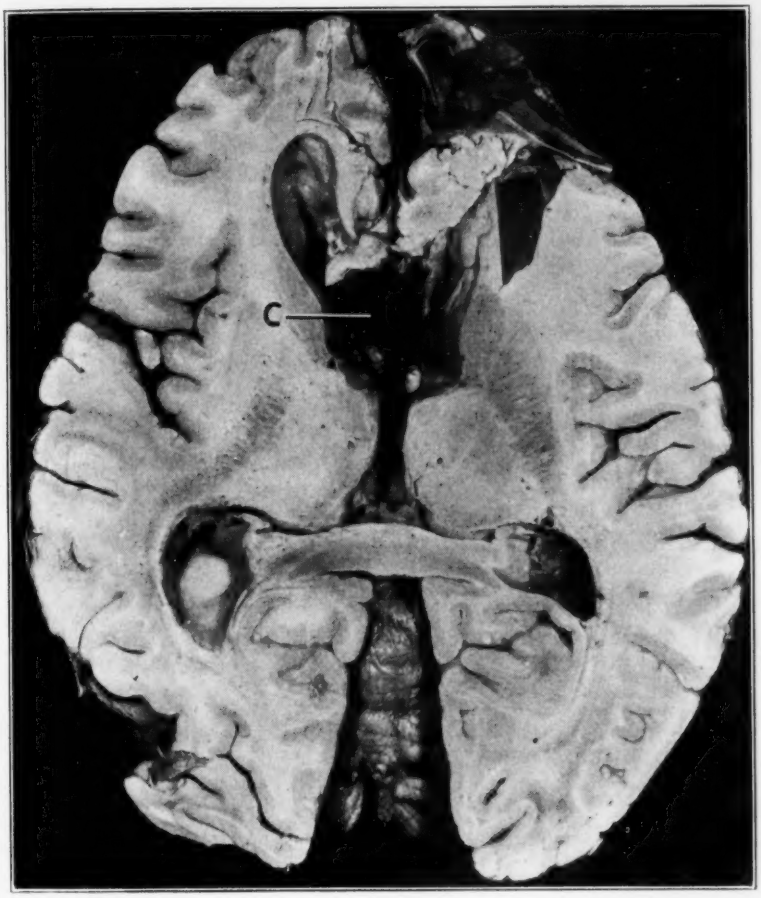

Fig. 6 (case 6).—Horizontal section of the brain showing soft and friable blood clot (indicated by *C*) situated between the anterior horns of the two lateral ventricles. This has remained unorganized, even after eight weeks. Ventricular dilatation is clearly seen. Markedly thickened and milky leptomeninges are well shown on the superior surface of the cerebellum. The cavity resulting from the operative removal is seen at the tip of the right frontal pole. The defect directly adjacent to this resulted from the removal of tissue for postmortem pathologic study.

The reactions in this case were associated with the presence of a protein-rich fluid at the operative site, which was demonstrated repeatedly by

puncture of the flap. The composition of this fluid was reported by the laboratory as being more nearly like that of blood than of spinal fluid.

In case 10 the reactions followed within twelve hours such significant events as sitting up in a chair and the manipulations associated with the first roentgen treatment. It is important to note that incident to such postural alterations intracranial pressure is reduced and the escape of a loculated irritant mass into the ventriculosubarachnoid system would be thereby facilitated. This occurrence was observed also in cases 11, 16, 20 and 21.

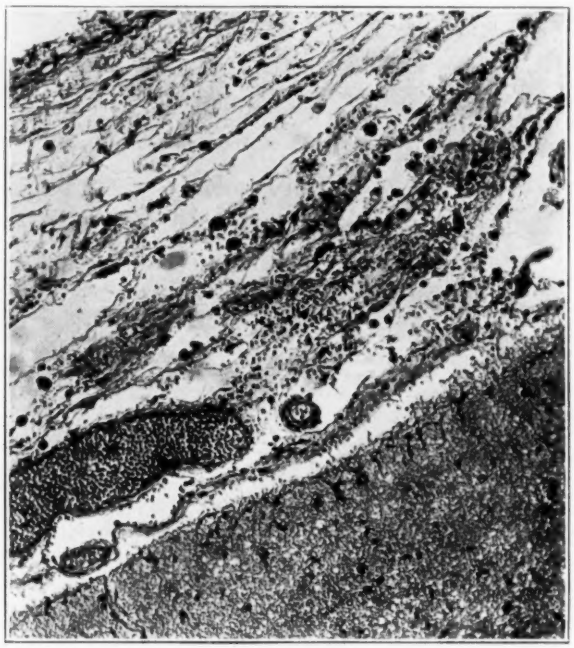

Fig. 7 (case 6).—Leptomeninges over the cerebral cortex showing fibrosis and cellular infiltration, indicative of chronic meningeal irritation. The macrophages here contained blood pigment. Hematoxylin-eosin-azure II stain; × 140.

The patient in case 10 died ten months later from recurrence of his glioblastoma multiforme. The relevant changes observed at autopsy consisted of generalized thickening of the arachnoid, orange-yellow pigment in the dura over the operative site and extensive recurrence of the tumor.

Aseptic leptomeningitis followed operative procedures in the posterior fossa in 10 cases. One of these is presented as typical.

Suboccipital Craniotomy with Subsequent Cystic Collections Among Neck Muscles of Fluid Related to Leptomeningeal Reactions.—Case 11.—J. K., a white man aged 22, who was admitted on Aug. 11, 1931, underwent a suboccipital craniotomy on Aug. 18 for midline medulloblastoma.

Postoperatively (fig. 8) a loculated cyst formed among the muscles of the neck at the site of a drain. In spite of pressure dressings this cyst continued to fill, and on the seventy-second postoperative day it became necessary to open the wound and attempt a better closure. Bits of cerebellum removed at that time gave no evidence of recurrence of tumor but did show perivascular infiltration with polymorphonuclear leukocytes and nests of leukocytes in the tissue. The surgeon noted that "when the cerebrospinal fluid pressure was low the cyst emptied into the spinal subarachnoid space, causing the reactions," The histologic evidence of inflammatory infiltration of the cerebellum adjacent to the cyst supported this view.

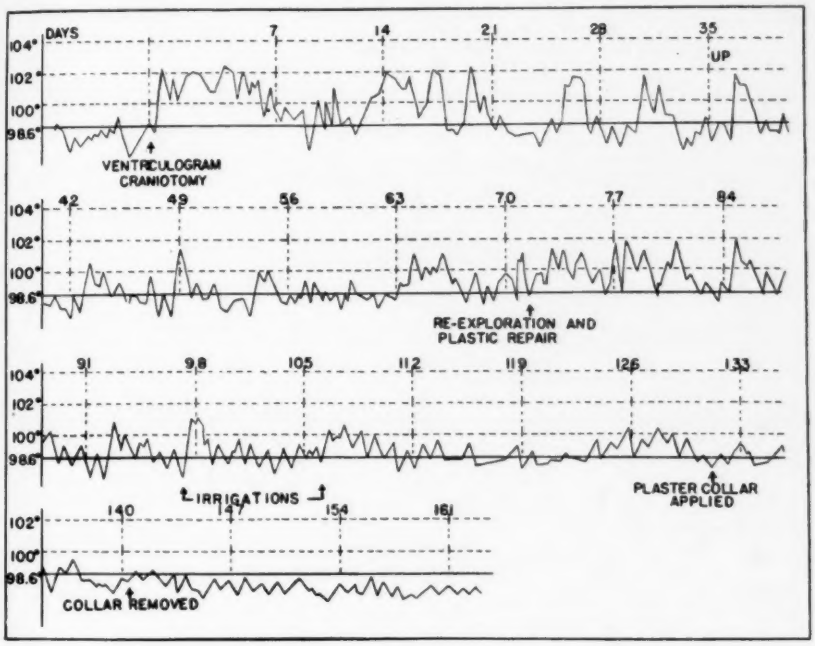

Fig. 8 (case 11).—The effect of application of a plaster collar to collapse cystic accumulations among the muscles of the neck is demonstrated.

In spite of the second operation the loculated cyst recurred, and meningitic reactions, although now mild, continued. Throughout this period fluid removed from the pseudomeningocele was persistently more yellow than that which was removed from the lumbar region at coincident punctures. A plaster collar for relief of pressure was applied on the one hundred thirty-first postoperative day, effectively collapsing the cyst and entirely relieving the meningeal signs and symptoms. From that time the temperature remained normal. All cultures of fluid made during the reactions were sterile.

In cases 12 and 13 there was also displayed a similar relation between the development of pseudomeningocele and irritative meningeal phenomena. From the observation that the meningeal reaction ceased on drainage of this fluid, with maintained collapse of the sac, and that with refilling of the sac meningitis shortly recurred, it may be stated that

there was some causal relation between the two. Although bacteriologic studies were inadequate it was evident that the condition in these 3 cases did not behave as would an infectious meningitis. Certainly the recurrent, intermittent type of reaction would not be seen if the meninges had been directly invaded by bacteria.

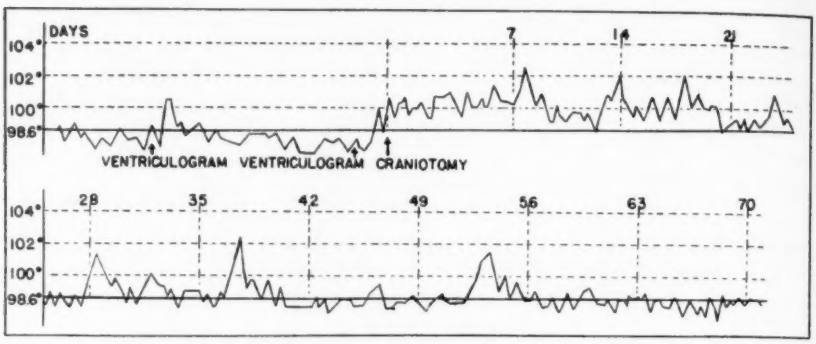

Fig. 9 (case 19).—Graphic record of temperature.

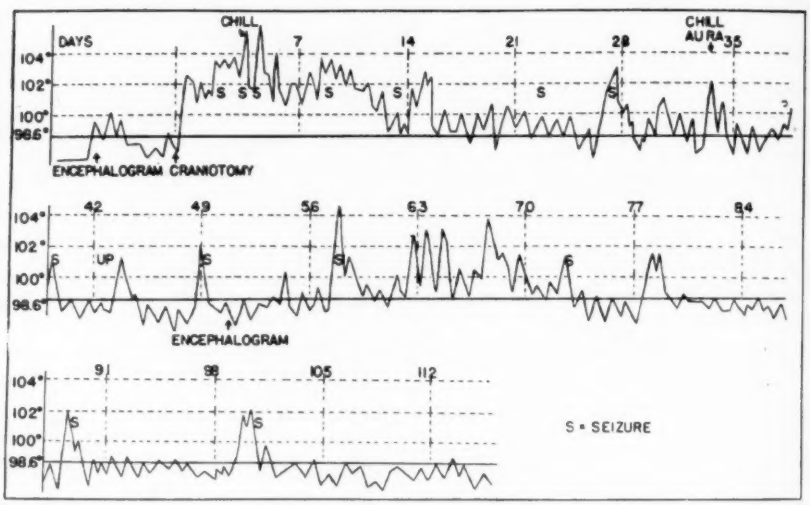

Fig. 10 (case 3).—Nearly every acute rise in temperature was preceded or accompanied by a seizure.

In not all the cases of suboccipital craniotomy in the group was there evidence of collections of fluid among the muscles. In several there was an excellent anatomic result in so far as the cervical musculature was concerned. In the 1 case of this sort that will be described the spinal fluid and blood probably became encysted at the operative site in the cerebellopontile angle.

Aseptic Reaction After Removal of Tumor from the Cerebellopontile Angle.—Case 19.—F. H., a white man aged 24, who was admitted on Nov. 29, 1933,

underwent a suboccipital craniotomy for removal of a perineurial fibroblastoma of the left fifth nerve. Intracapsular removal was carried out, and a drain was left within the remaining capsule of the neoplasm.

Postoperatively (fig. 9) he suffered attacks of mild, recurrent meningeal irritation with temperature spikes reaching almost 103 F., which occurred at intervals of five to nine days. With each of these episodes the patient felt "miserable," with headache, nausea and sometimes vomiting. The spinal fluid contained leukocytes varying in number from 500 to 3,500 per cubic millimeter. Two cultures

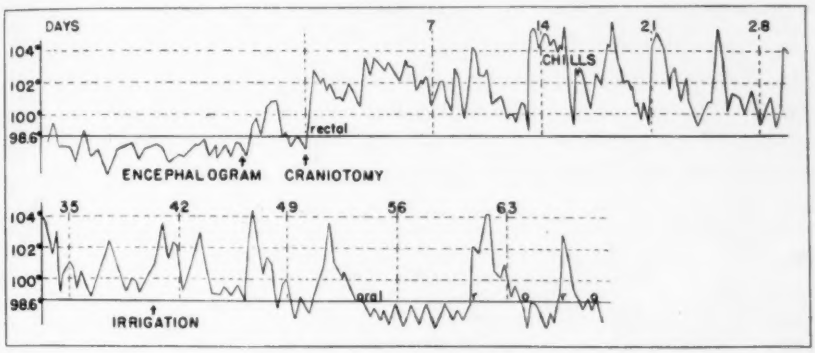

Fig. 11 (case 4).—In this instance craniospinal irrigation was carried out, with no change in the subsequent course.

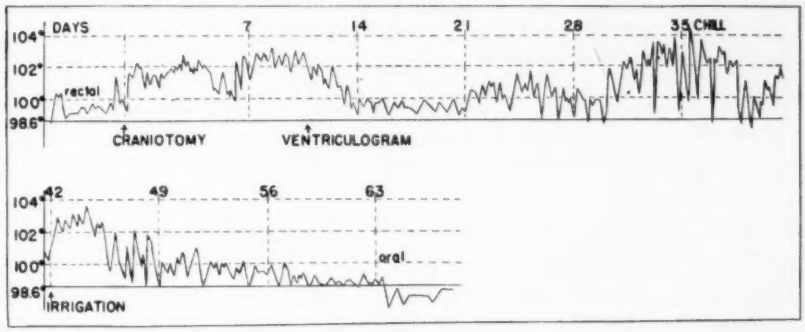

Fig. 12 (case 9).—Spinocranial irrigation on the forty-second postoperative day did not avert the incipient meningitic episode, but was not followed by any others.

were sterile. Another culture was reported as having grown Streptococcus viridans; however, this organism did not appear on the original plating, but only in broth.

After discharge the patient reported that he had had a repetition of the same sort of episodes he experienced in the hospital. This occurred on the third day at home and cleared up in two days with rest in bed.

In only 1 case in the series did the reaction follow an operative procedure on the spinal cord. A sterile meningeal reaction with no

readily demonstrable cause occurred. The remaining cases not presented in detail are summarized in table 1, which includes all the cases reviewed for this study.

ANALYTIC SUMMARY OF CLINICAL CASES

Of the series of 21 cases studied, the aseptic meningitis followed craniotomy in 20 and laminectomy in 1 only. Approximately 1,200 craniotomies were performed in the period covered by this study. Although some cases of leptomeningitis may have been overlooked in the review, the uncorrected incidence is roughly 1.6 per cent (table 2).

Tables 1 and 3 summarize data concerning the cases. It was concluded that it matters little whether a decompression is left with an open dura (15 cases) or whether the dura is closed (6 cases). Drainage through a stab wound for a day or two seemed to be unimportant in

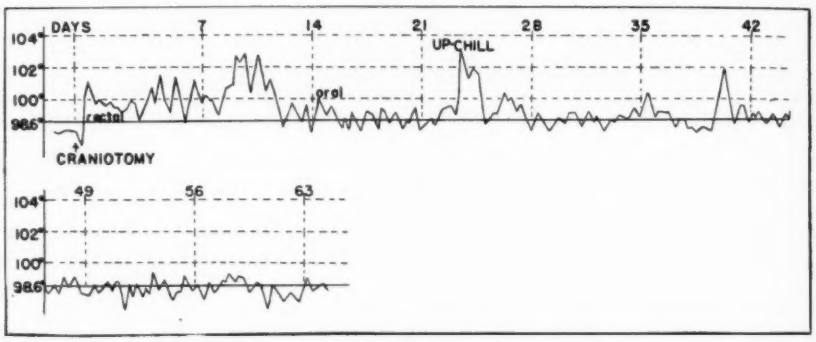

Fig. 13 (case 10).—This record represents one of the less severe reactions. The association between the patient's being up and the ensuing reaction is notable.

the case of supratentorial operation, but the impression was gained that the use of such drainage with suboccipital wounds was a factor predisposing to postoperative aseptic leptomeningitis, since the drain's presence seemed to facilitate leakage of cerebrospinal fluid into the cervical muscles, with formation of accumulations of fluid and clot-filled spaces. In 4 cases of suboccipital craniotomy the wound was not drained, although in 6 drainage was employed. The only 3 cases (11, 12 and 13) in which pseudomeningocele developed were among these 6.

The presence of an opening into the ventricular system is important in so far as it facilitates discharge of the irritating substances from the operative cavity. This situation existed in 8 of the 10 cases of supratentorial operation. In 1 of the remaining 2 instances (case 6) a postoperative encephalogram did not demonstrate filling of the operative cavity with air, although this failure did not exclude the possibility of communication of the cavity with either the ventricle or the subarachnoid space.

TABLE 1.—*Summary of Cases of Postoperative Aseptic Leptomeningitis*

TABLE 1.—*Summary of Cases of Postoperative Aseptic Leptomeningitis*

Case No.	Name	Age, Years	Sex	Lesion	Ventricle Left Open	Reaction Type	Cultures of Cerebrospinal Fluid		Days in Hospital	Illustrative Figure	Comment
							Number	Organism Found			
1	W. B.	26	M	Left frontal cystic scar	Left lateral probably	Recurrent	3 negative	.....	84	1	No removal at this operation
2	W. O'N.	24	M	Left frontal cystic scar	Left lateral	Severe; recurrent	14 negative	.....	91	2	
3	F. R.	20	M	Left frontal cicatrix	None	Severe; recurrent	5 negative	.....	126	10	
4	E. R.	22	M	Left frontal cicatrix	Left lateral	Severe; recurrent	5 negative	.....	85	11	Two positive cultures from skin flap; Staph. epidermidis and Str. viridans
5	O. M.	29	M	Left frontal cicatrix	Both lateral	Recurrent	8 negative 1 positive	Diphtheroid	80 died	3; 4	Organism considered nonpathogenic by bacteriologist
6	H. R.	37	M	Right frontal cystic cicatrix	None	Severe; recurrent	5 negative	.....	64 died	5; 6; 7	
7	M. Ja.	31	M	Right frontal scar	Right lateral	Mild	3 negative	.....	39	..	
8	M. Ju.	9	F	Right occipital scar	Right lateral	Mild	2 negative	.....	23	..	
9	V. E.	30	F	Right frontal astrocytoma	Right lateral	Severe; recurrent	9 negative	.....	75	12	One positive culture of skin flap; Staph. aureus and albus
10	F. McH.	26	M	Right parietal glioblastoma multiforme	Right lateral	Recurrent	2 negative	.....	67	13	
11	J. K.	22	M	Cerebellar medulloblastoma	None	Recurrent	3 negative	.....	173	8	
12	E. G.	24	M	Medulloblastoma, vermis cerebelli	Fourth	Recurrent	None	.....	47	..	
13	M. L.	11	F	Cystic astrocytoma, vermis cerebelli	None	Mild	1 positive	Staphylococcus aureus	25	..	Organism felt to have been a contaminant
14	W. W.	8	M	Cystic astrocytoma, of cerebellum	Fourth	Mild	3 negative	.....	40	..	
15	A. R.	18	M	Cystic astrocytoma, vermis cerebelli	Fourth	Severe; recurrent	5 negative	.....	81	..	
16	K. S.	25	M	Cystic astrocytoma, right cerebellar hemisphere	None	Recurrent	1 negative 1 positive	Diphtheroid	60	..	Organism ordinarily considered to be nonpathogenic
17	P. St. G.	45	M	Astrocytoma of aqueduct	Fourth	Recurrent	2 negative	.....	90	..	
18	C. L.	41	M	Cerebellar hemangioblastoma	None	Recurrent	None	.....	70	..	
19	F. H.	24	M	Perineurial fibroblastoma, left fifth nerve	None	Recurrent	2 negative 1 positive	Str. viridans	95	9	Organism felt to have been a contaminant
20	M. G.	44	M	Perineurial fibroblastoma, right fifth nerve	None	Recurrent	4 negative 2 positive	Micrococcus and diphtheroid	61	..	
21	W. F.	32	M	Meningoradicular adhesions (spina bifida occulta)	None	Recurrent	1 negative	.....	56	..	

In all the cases of infratentorial operation it was felt that the opening of the cisterna magna was responsible for providing a ready pathway for discharge of the irritant.

Whether the lesion removed was a tumor (12 cases) or an atrophic epileptogenic lesion (8 cases) did not seem to be significant, since the two were about equally represented. However, in only 2 cases was the tumor supratentorial. In each of the remaining cases, in which it was infratentorial, the cisterna magna was opened. In all the cases of

TABLE 2.—*Approximate Incidence of Aseptic Leptomeningitis Following Craniotomy*

Type of Craniotomy	Total Number of Cases	Cases of Aseptic Meningitis	Incidence, Percentage
All types	1,200	20	1.6
Excision of atrophic epileptogenic lesion	114	8	7.0
Removal of infratentorial neoplasm	134	10	7.0

TABLE 3.—*Analysis of Twenty Cases of Aseptic Leptomeningitis* *

	Supratentorial (10 Cases)	Infratentorial (10 Cases)
Nature of lesion		
Cicatrix	8	..
Tumor, cystic	..	4
Tumor, solid	2	6
Classification of tumors		
Astrocytoma	1	5
Medulloblastoma	..	2
Glioblastoma multiforme	1	..
Perineurial fibroblastoma	..	2
Hemangioblastoma	..	1
Lateral ventricle		
Opened	8	..
Not opened	2	..
Cisterna magna		
Opened	..	10
Wound		
Drained	3	6
Not drained	7	4
Remaining hemispheral defect		
Large	10	8
Small	..	2

* A case (case 21) of leptomeningitis following laminectomy is excluded.

cicatrix the lesion was, of course, in the cerebrum, and the ventricle was opened in 6 of the 8 cases. It may be regarded as significant, then, that for supratentorial procedures the incidence of meningeal reactions following removal of a tumor is low, while the complication more frequently follows the removal of a cicatrix.

This distinction is rendered more important by the fact that the 8 cases of excision of an atrophic lesion reported in this paper occurred in a series of 165 craniotomies performed on epileptic patients. The incidence here reaches 5 per cent, and if cases in which resection was not done are excluded it becomes 7 per cent (table 2). Consequently, aseptic leptomeningitis is an extremely important postoperative complication in the surgical treatment of focal epilepsy.

Since it has always been the practice in this clinic to avoid spilling the fluid of a cyst into the meningeal spaces, it is felt that cyst fluids were not responsible for this postoperative reaction. Moreover, since only 4 of the 12 tumors in this group were cystic, the irritating substance was not consistently the fluid of neoplastic cysts.

Thus, of prime importance are the situation of the lesion and the presence of a cystlike cavity resulting from its resection. In the majority of cases (18 of the 21) the reaction occurred in patients who suffered a relatively large loss of tissue at the time of operation. Consequently there resulted a fluid-filled cavity in which blood clot and the products of tissue destruction could accumulate and which communicated with the cerebrospinal fluid spaces, either through an open ventricle or through the cisterna magna.

Of the 21 patients, 4 died, and on all of these an autopsy was performed. In no instance was death ascribed directly to the aseptic meningitis, although in 2 (cases 5 and 6) it was undoubtedly contributory. In the other 2 cases death occurred ten and twelve months, respectively, after the operation as a result of recurrence of tumor, and the pathologic findings in these brains, other than the thickened leptomeninges and the partial obliteration of the subarachnoid space, were not contributory to the study of aseptic meningitis.

In all 3 cases (3, 5 and 6) in which preoperative and postoperative pneumographic studies were performed, late evidence of obliteration of the subarachnoid spaces and dilatation of the ventricular system was present, a finding consistent with the inflammatory reaction in the leptomeninges which followed the operative procedure and which was demonstrated at autopsy in the cases previously mentioned. In cases 5 and 6 the operative cavity filled with air, thus demonstrating the communication between the cavity and the ventriculosubarachnoid system. In case 3, on the other hand, such filling did not occur, so that a readily functioning communication was not demonstrated, although its presence was not necessarily excluded.

EXPERIMENTAL OBSERVATIONS

A large volume of experimental work has previously been done covering a wide variety of substances, all of which when introduced into the subarachnoid space can and do give rise to an aseptic inflammatory reaction which, clinically and pathologically, resembles completely a single episode of acute postoperative aseptic leptomeningitis.

Katzenelbogen [1] described this experimentally produced reaction as follows:

> Meningeal symptoms are more or less pronounced. In certain cases they may be accentuated, as happens in acute cerebrospinal meningitis. Being gen-

1. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood: A Physiological and Clinical Study, Baltimore, Johns Hopkins Press, 1935, pp. 379-380.

erally quite definite about five to six hours after the intraspinal injection, signs of meningitis commonly reach their maximal intensity between eight and twenty-four hours after spinal treatment, and, gradually receding, fade away completely within three to four days.

It is of interest that nearly any foreign substance introduced into the spinal fluid of experimental animals will cause at the least a mild meningeal reaction. Such an apparently innocent agent as physiologic solution of sodium chloride has been indicted for such action (Kasahara [2]). In the literature are many reports of severe meningitis following intraspinal injection of sterile, heterogenous serums in cases of tetanus (Ingleton [3]; Goldman [4]) or meningococcic meningitis (Goldman [4]). Similar aseptic meningitic reactions were at one time produced with therapeutic intent in the treatment of dementia praecox (Carroll, Barr, Barry and Matzke [5]; Katzenelbogen [1]).

Ample experimental evidence has already been established to substantiate the theory that postoperative aseptic leptomeningitis can be the result of an irritant substance introduced or discharged into the spinal fluid. The nature of the responsible irritant and its source are strongly suggested by study of the foregoing cases. Most of the patients showed evidence of an accumulation of blood at the operative site. On the basis of the hypothesis that an irritating substance was formed in these accumulations of blood, an experimental attempt was made to demonstrate the effects of injecting blood which had undergone degenerative change into the cerebrospinal fluid of animals.

GROUP 1.—*Cats given intracisternal injections of sterile fluid from a human subdural hematoma.*

Two previously normal cats received intracisternal injections of 1.5 cc. of sterile, brownish red fluid from a human subdural hematoma. Both these cats became obviously ill and were unusually quiet and retiring. Their rectal temperatures rose 3 degrees (F.), and when the animals were killed five hours later, the leptomeninges were found to be invaded to a marked degree by polymorphonuclear leukocytes, with smaller numbers of mononuclear cells.

A third cat received a similar injection of the same fluid but was allowed to live for twenty-four hours after the injection. This animal was also obviously ill, and its rectal temperature rose 3 degrees (F.). Again the leptomeninges were found to be the site of active inflammatory exudation. The changes are illustrated in figure 14 *A* and *B*.

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2. Kasahara, M.: Experimental Study in Meningeal Irritability, Am. J. Dis. Child. **28**:407-414 (Oct.) 1924.

3. Ingleton, A. T.: Aseptic Meningitis Following Intrathecal Injection of Antitetanic Serum, J. Roy. Army M. Corps **26**:234-235 (Feb.) 1916.

4. Goldman, D.: Serum Meningitis, Arch. Path. **9**:1027-1037 (May) 1930.

5. Carroll, R. S.; Barr, E. S.; Barry, R. G., and Matzke, D.: Aseptic Meningitis in the Treatment of Dementia Praecox, Am. J. Psychiat. **4**:673-703 (April) 1925.

It is extremely interesting that the infiltrating polymorphonuclear leukocytes were most intensely clustered about the fine blood vessels in the pia mater. This distribution is commonly seen in experimentally produced sterile meningitis (Finlayson and Latta [6]).

GROUP 2.—*Cats given intracisternal injections of sterile fluid from a human cerebellar astrocytoma (case 14).*

Two previously normal cats each received an intracisternal injection of 2.5 cc. of sterile fluid removed from the cyst of a cerebellar astrocytoma (clinical case 14). Only a slight rise in temperature resulted in each case (0.6 and 1.4 degrees [F.]), and the animals did not appear to be as ill as did those in group 1. Both these animals were killed six hours after the cisternal injection. Sections and spreads of the leptomeninges demonstrated an intense meningeal irritation which was entirely comparable to that shown by the cats in group 1. The number and distribution of the infiltrating cells in these animals were about the same as were observed in the animals in the first group. The protein content of the cyst fluid injected in these 2 cats was 5,020 mg. per hundred cubic centimeters, and the meningeal reaction was just as severe as that which resulted from injection of fluid from a subdural hematoma.

GROUP 3.—*Cats given intracisternal injections of sterile blood aspirated from a week old wound in the brain of the same animal.*

Three cats underwent sterile craniotomy for removal of the left occipital pole. This was accomplished by use of suction, and no effort was made to prevent postoperative bleeding into the site of removal. All the animals made a complete operative recovery. One week later fluid was aspirated from the operative cavity under sterile conditions and injected into the cisterna magna of the same animal from which the degenerating blood was obtained. In each instance spinal fluid obtained from the cisterna magna at the time of the injection was clear and colorless and contained no more than 4 white cells per cubic millimeter. Each animal was killed fourteen hours afterward, and another cisternal puncture was performed. Fluid thus obtained was cultured. In all cases no growth was obtained under either aerobic or anaerobic conditions.

Spreads and sections of the leptomeninges of these animals, however, revealed an intense meningitic reaction which was of the same nature and degree as that produced in the animals in group 1 and illustrated in figure 14 *A* and *B*.

In the experimental animals an intense aseptic leptomeningitis was found to follow the intracisternal injection of degenerating blood whether the blood was heterogenous, as in group 1, or autogenous, as in group 3. An identical, intense reaction resulted from injection of sterile cyst fluid from a human cerebellar astrocytoma.

These results confirm Essick's [7] experience with aseptic meningeal reactions. He expressed the belief that the greatest leptomeningeal

6. Finlayson, A. I., and Latta, J. S.: The Early Reaction in the Leptomeninges of the Rabbit to Trypan Blue, Anat. Rec. **78**:281-291 (Nov. 25) 1940.

7. Essick, C. R.: Formation of Macrophages by the Cells Lining the Subarachnoid Cavity in Response to the Stimulus of Particulate Matter, Contrib. Embryol. (no. 42) **9**:377-389, 1920.

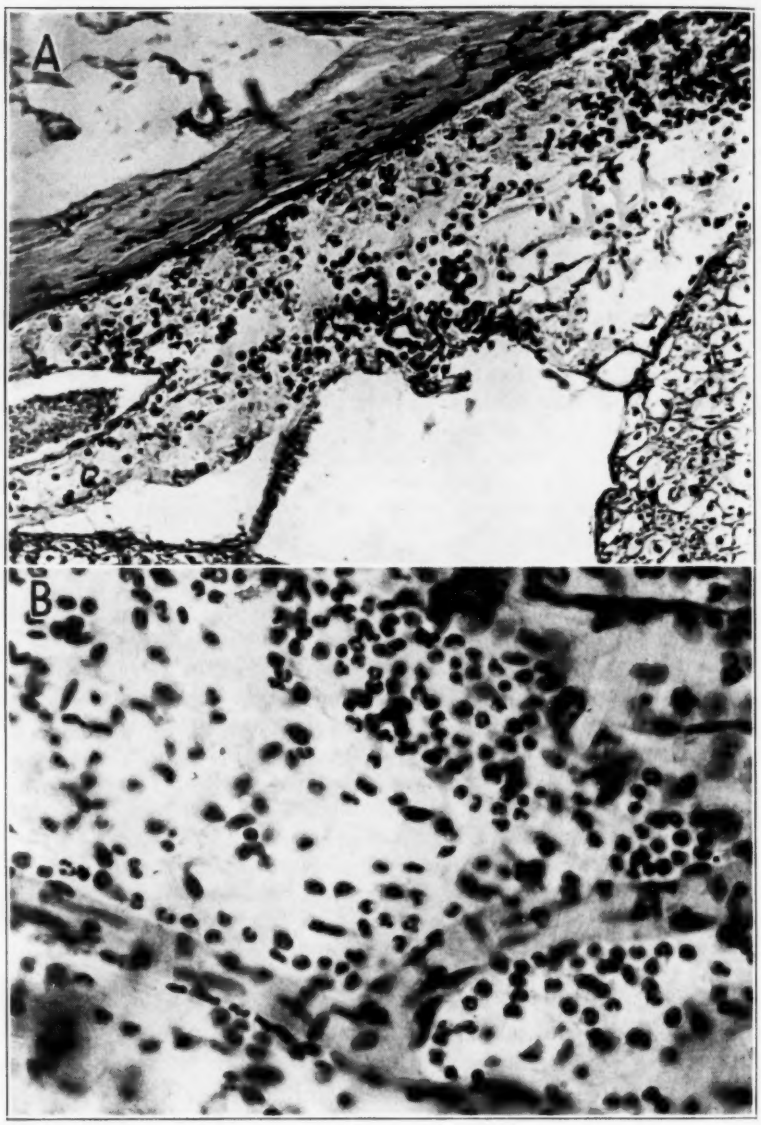

Fig. 14.—*A*, photomicrograph of a transverse section from the upper cervical region of the spinal cord of a cat given intracisternal injections of sterile fluid from a human subdural hematoma twenty-four hours before. Inflammatory infiltration of the leptomeninges is readily seen. Hematoxylin-eosin-azure II stain; × 218.

B, photomicrograph of a spread preparation of leptomeninges from the animal a section from the cord of which is shown in *A*. The exudative nature of the inflammatory reaction is apparent, and the close relationship of the infiltrating cells to the blood vessels is striking. Hematoxylin-eosin-azure II stain; × 488.

irritation resulted from the intracisternal injection of sterile laked blood obtained from the same animal.

It is felt, therefore, that the agent producing the irritative meningitis in the cases studied is undoubtedly formed in the blood accumulated in the operative cavity, although the continued formation of cystic fluid at the site of excision may be in part responsible.

PATHOGENESIS AND REVIEW OF LITERATURE

Acute postoperative aseptic leptomeningitis is a definite clinical entity which should be recognized and differentiated from true infectious meningitis. Of course either type may be encountered after operation, but the cause and the course of the two types of reaction are very different. It might be urged that these cases are but examples of septic meningitis which clears up spontaneously, since in cases 5, 9, 13, 16, 19 and 20 an occasional culture of spinal fluid or material drained from the wound yielded a growth of organisms. To disprove this assumption it may be pointed out that in 2 instances (cases 2 and 3) extremely careful and complete bacteriologic studies were conducted, with negative results. In regard to case 3, Prof. E. G. D. Murray reported that infection by any of the known pathogens had been excluded more than ordinarily well. Sterile cultures of spinal fluid by ordinary means were obtained in other cases. The aseptic nature of the leptomeningitis in the remaining cases in the group is suggested not only by its close clinical resemblance to the condition in the 2 carefully studied cases and its lack of resemblance to true infectious meningitis, but also by the fact that the patients recovered completely at a time prior to the dawn of modern chemotherapy. Furthermore, a plausible mechanism of the cause is proposed on a noninfectious basis.

In those instances in which positive cultures were obtained it was sometimes apparent from the way in which the organisms grew that contamination of the culture or of the fluid after the specimen had been obtained was extremely likely. The diphtheroids grown from the spinal fluid in cases 5, 16 and 20 were described by the department of bacteriology as of a type ordinarily considered nonpathogenic. In cases 13 and 19 the spinal fluid cultures were reported as showing evidence of contamination. In cases 4 and 9 positive cultures were obtained from fluid aspirated from the wound. Both were mixed cultures of the sort that might be expected from contamination from the skin during puncture of the wound.

The possibility that virus infection may be responsible for the condition is not considered likely, for the following reasons: Those recognized virus diseases affecting the central nervous system or its envelopes do not cause a purulent exudation but rather give rise to

relatively smaller numbers of lymphocytes and monocytes. The clinical course of such illnesses differs also in lacking the dramatic recurrent episodes so characteristic of the postoperative reaction. Thus, virus infection differs not only clinically but histopathologically from the syndrome presented here. It should be possible in the future to study the spinal fluid in such cases for the presence of virus; in the past lack of facilities made this impossible.

If, then, the syndrome is not due to bacterial or to virus infection, it must be of irritative origin. This view has been most frequently upheld in the few reports of postoperative aseptic meningeal reactions which have appeared in the literature. In none of these reports was the possibility of bacterial infection considered once negative cultures had been obtained.

The earliest discussion of sterile meningitis following operations on the brain is found in consideration of operative intervention in the case of craniocerebral epidermoids or cholesteatomas. In 1924 Bailey [8] reviewed the literature dealing with Cruvelhier's pearly tumors, but failed to find any instances in which meningitis followed removal of the tumor, although he described a case of his own in which such an event occurred.

Cushing and Bailey,[9] in their book entitled "Tumors Arising from the Blood-Vessels of the Brain," described a case which appears to be exactly similar to the cases presented in this study. On the ninth day after the removal of a cerebellar hemangioblastoma in their case XV, the patient "had a febrile upset with leucocytosis and considerable fulness of the suboccipital region which was relieved by lumbar puncture. The fluid was sterile to culture. There were five other similar periodic rises in temperature during the course of the next month, all clinically alike and accompanied by slight headache, fulness and pulsation in the suboccipital region. Each succeeding rise was less than the preceding and of shorter duration. (We were at the time unfamiliar with the fact that these waves of pyrexia suggesting meningitis are not uncommon after cerebellar operations.)" The patient made an otherwise satisfactory recovery.

Critchley and Ferguson [10] reported the occurrence of fatal sterile meningitis in 3 of 7 cases of cholesteatoma in which they performed operation. Precisely the same course as they described was observed in cases 5 and 6 in the present study, in which death also occurred

8. Bailey, P.: Further Observations on Pearly Tumors, Arch. Surg. **8**:524-534 (March) 1924.

9. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1928, p. 110.

10. Critchley, M., and Ferguson, F. R.: The Cerebrospinal Epidermoids (Cholesteatomata), Brain **51**:334-384, 1928.

approximately two months after operation. These authors expressed the belief that the cause was irritation of the meninges resulting from toxic material within the tumor itself. Furthermore, they maintained that secondary meningitis was of sufficiently frequent occurrence to call for excessive care in the removal of this type of tumor in order to prevent the contamination of the neighboring structures with its toxic contents.

Further cases of this sort of meningeal reaction during the convalescence following removal of a cholesteatoma have been reported by Sachs,[11] Olivecrona [12] and Love and Kernohan.[13] It is of interest that in the case reported by Sachs,[11] as in cases 10, 11, 16, 20 and 21 of this study, the reaction followed the patient's first effort to get out of bed. Here, the tumor removed was thought to be a cholesteatoma and was situated in the pineal region.

Krieg,[14] in a more recent review of literature relating to the epidermoid tumors, found occasional meningeal reactions following their removal. He reported that Hofmeister, Armour, Foerster and Max Meyer had each described cases in which operative removal of a cholesteatoma was followed by sterile meningitis, and he suggested that the more fluid were the contents of the cyst the more widely were they apt to be dispersed and the greater would be the ensuing reaction. It was his impression that the cholesterol or other acid breakdown product of the cholesteatoma was responsible for the irritative meningitis.

Although postoperative aseptic meningitis has been more frequently recorded in relation to cholesteatoma, the syndrome has been described as following the removal of several other types of tumors. Olivecrona [15] described 5 cases of typical sterile meningitis following removal of meningioma. He related its cause to the use of electrocautery in stopping bleeding from the bone flap. The thought occurred to him that since in none of these cases was the dura closed, the coagulated bone produced an irritant substance which, discharged into the spinal fluid, was responsible for the reactions. Because of this belief, he subsequently gave up the use of electrocautery in securing hemostasis in the bone flap in such operations.

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11. Sachs, E.: The Diagnosis and Treatment of Brain Tumors, St. Louis, C. V. Mosby Company, 1931, p. 276.

12. Olivecrona, H.: On Suprasellar Cholesteatomas, Brain **55**:122-134 (March) 1932.

13. Love, J. S., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of Central Nervous System, J. A. M. A. **107**:1876-1883 (Dec. 5) 1936.

14. Krieg, W.: Aseptische Meningitis nach Operation von Cholesteatomen des Gehirns, Zentralbl. f. Neurochir. **1**:79-86, 1936.

15. Olivecrona, H.: Die parasagittalen Meningeome, Leipzig, Georg Thieme, 1934, pp. 142-143.

Both Merrem [16] and Tönnis [17] independently described a similar condition in 1936. Merrem, after studying 3 patients in whom aseptic meningitis resulted from the removal of a cystitc neoplasm, decided that the condition resulted from incomplete removal of the tumor and cyst wall.

Aseptic meningitis, then, has been relatively infrequently described as a postoperative neurosurgical complication, and the suggested cause of the reaction offered by each authority differs. Fundamentally, nevertheless, each expressed opinion as to the cause of the postoperative meningeal reaction agrees that the condition is the result of an irritant produced or released by the operative intervention.

Evidence accumulated in the review of the cases presented here strongly favors the theory that bloody fluid accumulating at the site of the operative cavity or among the muscles of the neck undergoes degenerative change with the formation of substances which, when discharged periodically into the general subarachnoid space under conditions of altered cerebrospinal hydrodynamics, produce severe meningeal symptoms and signs.

Many of the patients showed marked evidence of continued postoperative hemorrhage within the wound. This manifested itself either in the formation of hematoma in the subaponeurotic space (cases 2, 4 and 9), associated with gradually increasing spinal fluid pressure in the first twenty-four to forty-eight hours, or by the presence of red blood cells in the lumbar spinal fluid in more than the numbers usually observed after operation. In none of the cases was the increasing pressure or the number of red cells in the fluid of a degree sufficient to require reopening of the wound.

The observation that postoperative aseptic leptomeningitis rarely follows extirpation of a supratentorial neoplasm, while it more commonly is a complication after resection of an atrophic epileptogenic lesion of the cerebral hemispheres, may be readily explained on the basis of the theory presented. The elevated intracranial pressure persisting after the removal of a supratentorial tumor effectively collapses the resulting cavity unless it is extremely large (cases 9 and 10). A meningocerebral cicatrix, on the other hand, being unassociated with increased pressure, sets the stage for ensuing meningeal reactions by permitting the operative defect to remain open. Blood readily accumulates therein and, after undergoing degenerative changes, easily finds its way into the cerebrospinal fluid.

That a blood clot situated in such an operative cavity undergoes degenerative and liquefactive changes has been shown in those cases in

16. Merrem, G.: Ueber aseptische postoperative Meningitis bei cystischen und zerfallenden Blastomen, Deutsche Ztschr. f. Chir. **247**:105-112, 1936.

17. Tönnis, W.: Aseptische Arachnoiditis nach Hirnoperationen, Arch. f. klin. Chir. **186**:375-377, 1936.

which puncture of the cavity was carried out. Brownish yellow fluid, of high protein content and usually containing cellular debris, could be demonstrated in this manner. Chemical studies carried out on such fluid in 2 cases (4 and 9) demonstrated that its properties resembled more nearly those of blood than those of spinal fluid.

The arachnoid membrane normally forms a complete barrier to the passage of this irritating fluid, doubtless because the fluid contains protein molecules too large to pass through the membrane (Penfield [18]). The constitution of the cerebrospinal fluid (Boyd [19]; Greenfield and Carmichael [20]; Merritt and Fremont-Smith [21]) depends on the integrity of the leptomeningeal barrier. A subdural hematoma outside the arachnoid stains this structure but does not produce hyperthermia or reaction unless communication is established with the subarachnoid space. If the fluid that is formed in a subdural hematoma of long standing is aspirated at operation and injected under sterile conditions into the cisterna magna of an animal, there is an immediate febrile reaction on the part of that animal. Similarly, if the fluid is withdrawn from a chronic cystic tumor of the cerebellum (case 14) and injected into an animal, that fluid, which had previously been held back, perhaps by a thin membrane, proves to be extremely irritating in the subarachnoid space of the animal.

If blood can produce an aseptic meningitis, why then is not such a reaction the rule in cases of spontaneous subarachnoid hemorrhage? Primarily, the blood in a subarachnoid hemorrhage is neither laked nor broken down into its component proteins. Thus, there is a fundamental difference in the two situations, and not until such time as the blood of a subarachnoid hemorrhage had undergone degenerative change would such an acute episode occur as is seen in cases of postoperative aseptic meningitis. Furthermore, by the time such degeneration has occurred the greater part of the extravasated blood has already been absorbed through the usual channels, since, according to evidence obtained by Sprong,[22] 71 to 75 per cent of the blood cells injected into the subarachnoid system of a dog disappear from the fluid within sixty to ninety minutes from the time of their introduction. In the animals studied by

18. Penfield, W.: Subdural Effusion and Internal Hydrocephalus, Am. J. Dis. Child. **26**:383-390 (Oct.) 1923; The Cranial Subdural Space, Anat. Rec. **28**:173-175 (July) 1924.

19. Boyd, W.: Physiology and Pathology of the Cerebrospinal Fluid, New York, The Macmillan Company, 1920.

20. Greenfield, J. G., and Carmichael, E. A.: The Cerebrospinal Fluid in Clinical Diagnosis, New York, The Macmillan Company, 1925.

21. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1938.

22. Sprong, W.: The Disappearance of Blood from the Cerebrospinal Fluid in Traumatic Subarachnoid Hemorrhage, Surg., Gynec. & Obst. **58**:705-710 (April)1934.

him polymorphonuclear leukocytes did not appear in considerable numbers until twenty-four hours after the subarachnoid injection. This period is considerably longer than that observed in the experimental work described in this paper, as well as in previous studies on irritative meningitis. Katzenelbogen [1] described meningitis as resulting within five to six hours of subarachnoid injection of irritants.

Bagley [23] also observed that the onset of meningeal signs and symptoms following subarachnoid hemorrhage was delayed as much as several days. In 1928 he reported experimental and clinical evidence of chronic meningitis in the dog and in man following repeated injections of blood in the former and spontaneous or traumatic bleeding in the latter. He described the course of such a condition in the human subject as follows:

> The most important signs and symptoms in patients with a small quantity of blood usually appear after an interval of a few days and are due to the reaction of the meninges. This state is characterized by headache of a neuralgic type, delirium, mild elevation in temperature, slight increase in pulse rate, postcervical rigidity and a positive Kernig sign. These symptoms may gradually subside as the blood is absorbed.

As is readily seen in the temperature graphs, nearly all the patients in this series had a low grade, persistent fever during the first week or ten days after the operation and before the first acute meningeal episode. The statement cited from Bagley's article offers a satisfactory explanation for the immediate slight elevation of temperature, and probably accounts for the low grade fever continued beyond the fifth postoperative day in many cases. The later, more acute and greater elevations are the result of the sudden entrance into the spinal fluid of degenerating blood from the operative cavity.

PREVENTION AND TREATMENT

Inasmuch as the condition is caused by accumulations of blood that connect with or discharge into the subarachnoid space, prevention calls for (1) careful hemostasis and (2) avoidance of connections with the subarachnoid space which are apt to remain open.

Hemostasis is the constant care of every neurosurgeon and calls for no particular discussion here. The practice of drainage through a stab wound in the scalp and insertion of a rubber dam drain down to the site of operative removal has not seemed to affect the incidence of postoperative aseptic meningitis except as it influences the formation of pseudomeningocele in cases of suboccipital craniotomy.

Opening the arachnoid at points over the convexity of the brain, as is usual in intracranial operations, does not leave a permanent fistula. If small openings are made in the large cisterns or in the lateral

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23. Bagley, C.: Blood in the Cerebrospinal Fluid: A. Experimental Data, Arch. Surg. **17**:18-38 (July) 1928; B. Clinical Data, ibid. **17**:39-81 (July) 1928.

ventricles, these connections likewise seem to close. On the other hand, openings into the subarachnoid space that do result in trouble are of two chief types. Above the tentorium, a large opening into the ventricle, such as results from large amputation of an atrophic lesion in the frontal lobe or from extensive removal of a neoplasm, provides a ready pathway for passage of fluid from old blood down through the ventricles into the cisterna magna. In such cases there seems to be no histologic reaction of the ependymal walls (cases 5 and 6). The irritation and thickening first appear in the leptomeninges.

Below the tentorium, easy entrance into the cerebrospinal fluid spaces results when a wide opening into the cisterna magna has been made. Such an opening was present in all the cases of infratentorial craniotomy. Cushing has pointed out that wide openings in the arachnoid over the great cistern sometimes result in postoperative fever. His custom of leaving the dura over the cerebellum unclosed would have made it still more necessary to have an intact arachnoid barrier.

The irritant substances, then, reach the subarachnoid space either directly, through the cisterna magna, or indirectly, by way of the ventricular system.

Postoperative aseptic meningitis even after it occurs does not present great danger, but it is troublesome and disturbing and can probably be avoided by conservatism in opening the ependymal wall of the ventricle above the tentorium and the cisterna magna below it.

Prevention, thus, depends on hemostasis and proper closure of wounds, more especially on the avoidance of an internal fistula or persisting communication between the degenerated blood clot and the subarachnoid space.

Once the condition has become well established, an effort may be made to evacuate the blood clot by simple puncture of the wound and aspiration of the degenerating blood which is present. In rare occasions it may be accomplished by washing out the cavity by making simultaneous punctures of the wound and the lumbar portion of the spinal canal with subsequent spinocranial irrigation. Sterile Ringer's solution (Kasahara [2]; Weed and Wegeforth [24]) was used for through and through irrigation between the lumbar subarachnoid space and the wound in cases 1, 4 5 and 11, with no apparent benefit. The reason for this failure probably was the fact that semisolid portions of clot remained behind, as was shown at autopsy in case 6. Should a cavity exist within the suboccipital muscles, an elastic pressure bandage may be used to close the space and stop the recurring bouts of fever.

In most of these cases nothing was done except to wait in exasperation until the situation cleared up by itself, which it seems to do within

24. Weed, L. H., and Wegeforth, P.: Experimental Irrigation of the Subarachnoid Space, J. Pharmacol. & Exper. Therap. **13**:317-334 (July) 1919.

two months. The procedure of reopening the wound to evacuate the clot from the cavity was not resorted to, and probably should not be unless there are other indications for it.

SUMMARY AND CONCLUSIONS

A syndrome of acute postoperative aseptic leptomeningitis has been described and 21 cases have been reviewed. Although some instances may have been overlooked during the review, the recorded incidence was 1.6 per cent in 1,200 craniotomies of all kinds and 7 per cent in 134 suboccipital craniotomies with resection of tumor. It occurred after 7 per cent of 114 radical excisions of large atrophic epileptogenic lesions of the cerebral hemispheres.

The condition first appears about seven to ten days after craniotomy and is characterized by acutely recurring episodes of fever, stiff neck, headache and at times mental confusion. Although the cerebrospinal fluid is at such times flooded with polymorphonuclear leukocytes, cultures of the spinal fluid characteristically remain sterile. Virus infection has been suggested, but efforts to demonstrate such cause have failed. On the other hand, claims for a chemical mechanism can be substantiated.

The mechanism in the cases reviewed for this study appears to be as follows: There persists after operation a cavity at the site of operation, particularly when removal of a neoplasm or scar has been extensive. This fills with blood clot, and the clot subsequently undergoes liquefaction and degeneration. Its products, high in protein, accumulate and are periodically discharged into the general subarachnoid space, either indirectly, through a ventricle which has been opened by the operative procedure, or directly, through subarachnoid channels from the cisterna magna.

Reference to sporadic cases described in the literature and to experimental work amply supports this concept. It has been shown that single episodes of the syndrome can be reproduced by means of experimental injection of products of degeneration of blood clot, as well as of yellow cyst fluid, into the cisterna magna of experimental animals. Animals so treated became obviously ill and suffered elevations of temperature, and at autopsy intense polymorphonuclear leukocytic infiltration was found in the leptomeninges.

The arachnoid membrane is normally an effective barrier to the passage of subdural fluid which is high in protein, although easily diffusible crystalloids pass through it with ease. A persisting internal fistula from operative wound to subarachnoid space is responsible for periodic postoperative aseptic meningitis and also, in some cases, for the low grade, continuous fever that may follow intracranial operations.

PATHOLOGIC AND MENTAL ALTERATIONS IN A CASE OF SIMMONDS' DISEASE

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REVIEW OF LITERATURE

Seven years after Paulesco [1] described the train of symptoms which followed the experimental removal of the pituitary gland in dogs, Morris Simmonds, a Hamburg physician, demonstrated the relationship of destruction of the anterior lobe of the pituitary gland to the clinical picture of pituitary cachexia which now bears his name.[2] Since this time over 200 cases have been reported in the literature, but only one third of these have been verified by autopsy. In 1938, Lisser and Ascarilla [3] collected 69 pathologically verified cases. As a result of a detailed statistical study of these cases they suggested four cardinal characteristics on which the clinical diagnosis of Simmonds' disease should be based: viz., loss of weight, frequently progressing to emaciation; diminished sexual function, manifested by amenorrhea and loss of libido in the female and by loss of libido and potency in the male; marked asthenia, and a profoundly lowered basal metabolic rate.

The pathogenesis of the destruction of the anterior lobe of the pituitary has been variable, even in the cases reported by Simmonds.[4] Among the types of lesions reported are cysts and solid tumors of the pituitary, intracranial syphilis and tuberculosis, trauma to the base of

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From the Metropolitan State Hospital, Waltham, Mass., and the Department of Pathology, Tufts College Medical School, Boston.

1. Paulesco, N. C.: L'hypophyse du cerveau, Paris, Vigot Frères, 1908.

2. Simmonds, M.: Ueber Hypophysisschwund mit tödlichem Ausgang, Deutsche med. Wchnschr. **40**:322-323, 1914.

3. Lisser, H., and Ascarilla, R. F.: The Clinical Diagnosis of Simmonds' Disease (Hypophyseal Cachexia): A Critical Statistical Comparison of Sixty-Nine Verified and One Hundred and Thirty-Four Unverified Cases, Tr. A. Am. Physicians **53**:210-220, 1938.

4. Simmonds, M.: Ueber Kachexie hypophysären Ursprungs, Deutsche med. Wchnschr. **42**:190-191, 1916; Atrophie des Hypophysisvorderlappens und hypophysäre Kachexie, ibid. **44**:852-854, 1918; footnote 2.

the skull and acute inflammatory processes. The most common lesion, however, is scarring or atrophy of the anterior lobe, with little or no evidence of the etiologic factors in its production. In most of the cases the destruction has been attributed to thrombosis or embolism of the arteries supplying the pituitary gland. The frequent association with childbirth has been emphasized, and various explanations of the pathogenesis have been suggested. Among these are bacterial embolism resulting from septicemia and thrombosis associated with the sudden decrease in the size of the pituitary gland in the puerperium. In 1937 Sheehan [5] reported 11 cases of death in the puerperium in which acute necrosis of the anterior lobe of the pituitary was present. He expressed the belief that he was dealing with thrombi formed in situ which were probably not septic in origin, but were produced by the sudden change from hypertrophy to involution in the anterior lobe occurring rapidly after delivery. He emphasized the possible importance of similar lesions in the production of Simmonds' disease.

Mental changes associated with pituitary cachexia were reported, prior to Simmonds' classic report, by Austregesilo, Pinheiro and Marques,[6] whose patient had mental symptoms three years prior to admission to the hospital. The patient was of a low intellectual level, was well oriented and did not exhibit impairment of memory. He experienced visual and auditory hallucinations, which, at times, were of a penal character. He saw Negroes who tortured him and recalled to him the evil deeds of his past life. His ideas of persecution were poorly systematized.

The patient in Jakob's second case [7] was disoriented and delirious, had visual and auditory hallucinations, with hardly any spontaneous talking, and responded to questions with weak and dragging speech.

Psychic changes, such as apathy, depression or somnolence, have been reported in approximately one half of the verified cases of Simmonds' disease [3] and may be an additional stumbling block in the clinical differentiation of this condition from anorexia nervosa. In contrast to the rather detailed reports and analyses of the mental picture in cases of anorexia nervosa, little or no stress has been placed on the details of the psychiatric picture in most of the cases of Simmonds' disease in which mental aberrations have occurred. Neurologic signs

5. Sheehan, H. L.: Post-Partum Necrosis of Anterior Pituitary, J. Path. & Bact. **45**:189-214, 1937.

6. Austregesilo, A.; Pinheiro, M., and Marques, E.: Sur un cas de syndrome pluriglandulaire endocrinique, Encéphale **14**:150-156, 1913.

7. Jakob, A.: Zwei Fälle von Simmondsscher Krankheit (hypophysäre Kachexie) mit besonderer Berücksichtigung der Veränderungen in Zentralnervensystem, Virchows Arch. f. path. Anat. **246**:151-182, 1923.

are not infrequent in the terminal phase of the illness and are probably most frequently associated with hypoglycemic shock.

In spite of the frequent presence of psychic changes and neurologic abnormalities, in many case reports the central nervous system has been described as showing nothing significant or as not having been examined. The case of Lang [8] in which the condition clinically resembled Simmonds' disease but autopsy revealed a normal pituitary and a cystic tumor of the infundibulum is a stimulus to search for more information regarding the relationship between the pituitary and the hypothalamus. In 1923 Jakob [7] emphasized the importance of changes in the central nervous system. He described circumscribed dropping out of ganglion cells (*Verödungen*) with some glial reaction in the cerebral cortex, especially in the temporal lobe. Larger areas of glial nests were observed in the cornu ammonis. Atypical glial forms were seen not only in the cortex but also in the striatum, thalamus and nuclei of the pons. Severe degenerative changes were described in the dentate nuclei and the inferior olives. Jakob reported similar lesions in a case of Addison's disease. Gallavan and Steegman [9] reported changes similar to those described by Jakob, but failed to find involvement of the inferior olives and dentate nuclei. They reported diffuse shrinkage in the cortical cells and argentophilia of the nuclei in the cortical cells of the second, third and fourth layers. They observed periarterial collars of fat-filled gitter cells and scattered deposits of hemosiderin. In the supraoptic nucleus there was some loss of cells, and in the tuber cinereum, total loss of axis-cylinders coming from the pars nervosa of the pituitary gland. The paraventricular nucleus was not reduced in size.

Recently Kotte and Vonderahe [10] have reported similar changes in the hypothalamus of a diabetic patient who after infarction of the pituitary revealed the Houssay phenomenon. In this case there was rather marked subependymal gliosis.

Weiner [11] did not observe necrobiosis or other cell changes in the hypothalamus but found generalized congestion and edema with ischemic changes in the mamillary bodies. There were focal patches of necrosis

8. Lang, F. J.: Ein Plattenepithelzystopapillom (Erdheimscher Hypophysengangtumor) des Infundibularbereiches mit hypophysärer Kachexie, Wien. klin. Wchnschr. **37**:977-979, 1924.

9. Gallavan, M., and Steegman, A. T.: Simmonds' Disease (Anterior Hypophysial Insufficiency): Report of Two Cases with Autopsy, Arch. Int. Med. **59**:865-882 (May) 1937.

10. Kotte, J. H., and Vonderahe, A. R.: The Houssay Phenomenon in Man: Report of a Case of Diabetes Mellitus, Infarct of the Anterior Lobe of the Pituitary Body and Terminal Hypoglycemia, J. A. M. A. **114**:950-953 (March 16) 1940.

11. Weiner, H. A.: Simmonds' Disease: Report of a Case, Yale J. Biol. & Med. **10**:31-39, 1937.

with glial proliferation in the medulla and extensive collections of lymphocytes and plasma cells in the leptomeninges and perivascular spaces. In the last 3 cases (Gallavan and Steegman,[9] Kotte and Vonderahe [10] and Weiner [11]) there was clinical evidence of hypoglycemic shock.

The following case of Simmonds' disease is presented because of the unusual changes in the pituitary gland, the presence of an associated psychosis and the significant lesions in the central nervous system.

REPORT OF CASE

Past History.—C. S., the youngest of 4 children, was born in Baltimore in 1889. She was considered a bright girl in school and worked as a stenographer and typist until her marriage, at the age of 37. She was happy, sociable, friendly, active and had many interests. She was somewhat sensitive and quick tempered, but had many friends. At the death of her father, when the patient was 23, she had a period of depression, which lasted three months. At the death of her mother she was again depressed and had to go away for a rest. The patient's menses began at the age of 14 and were of a twenty-eight day cycle, lasting three to four days, with medium flow and no pain.

Present Illness.—There were no serious illnesses until the birth of her only child, one year after marriage. The details of the labor, delivery and puerperium are incompletely recorded. Delivery was by forceps, and the patient sustained a tear, which was repaired. On the day of delivery she was given "four doses" of caffeine with sodium benzoate, which suggests that some degree of shock was associated with the delivery. The postpartum course was marked by twelve days of elevated temperature, which reached a peak of 103 F. on the fifth day. She remained in the hospital for three weeks and was prostrated for a considerable part of that period, complaining of weakness even at the time of her release. After delivery she steadily lost weight and failed to regain her strength. Her menstrual periods ceased for nine months. The subsequent menstrual periods were irregular and were accompanied by fainting spells and dysmenorrhea. Eventually her periods ceased altogether.

Mental symptoms appeared at the first postpartum period, in September 1927. She became depressed and overreligious, attended church services frequently, prayed considerably and talked incessantly about saints and angels. She felt that she was being punished for some sin, presumably that of not being good to her parents when they were alive. She was thought to be hallucinated in the auditory field and expressed suspicions of infidelity of her husband. She was despondent and pessimistic about the future and was finally committed to Danvers State Hospital, on April 19, 1928. The diagnosis of manic-depressive psychosis, depressive type, was made.

In July 1936 she was transferred to the Metropolitan State Hospital, where the psychiatric picture was essentially one of depression and diminished psychomotor activity. She was quiet and soft spoken; her voice at times was scarcely audible. Her conversation was coherent and relevant, but responses were retarded. She was not friendly toward the other patients, but this was the result of lack of initiative rather than of definite antagonistic feelings. Her memory was good for the remote and recent past. She was able to give an accurate account of her life history and her hospitalization, although this information came haltingly and after many direct

questions. There was a mild paranoid trend. The patient admitted that she held her husband responsible for her long stay in the hospital and retained ideas of his unfaithfulness. She also intimated abusive treatment at the previous hospital but refused to be specific in her complaints. She stated when she was first admitted that things seemed unreal and mixed up. No history of hallucinatory experiences was obtained at any time. She showed some insight and stated that the peculiar feelings of unreality which she had experienced in the beginning had disappeared and were due to her imagination and to her upset mental condition. Although her fund of general information was fairly good, her contact with current events was poor, as she took little interest in world happenings. Orientation was accurate. Although there was some improvement in her mental condition after administration of thyroid, she remained essentially depressed and retarded. She had rather frequent crying spells and felt that she was in everybody's way and that she was no good to any one. Although she recognized that death would have been a solution to her problem, she denied having any suicidal thoughts.

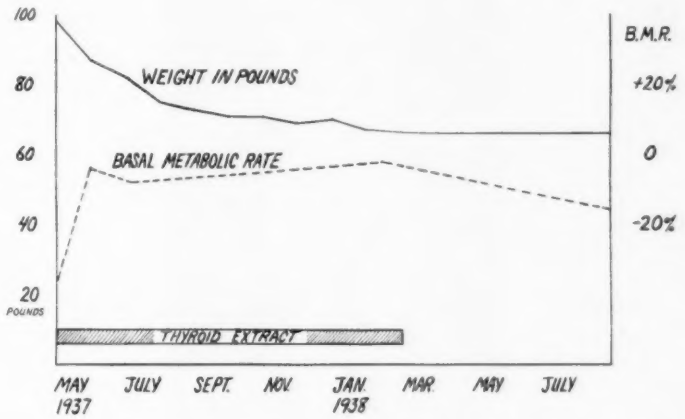

Fig. 1.—The effect of desiccated thyroid, 1 grain twice a day, on the body weight and the basal metabolic rate.

Physical Examination.—She was small, thin and pale. Pubic and axillary hair was practically absent. The hair of the scalp was dry and lusterless; the skin was thick, dry and scaly. The thyroid gland was not palpable. The blood pressure was 170 mm. of mercury systolic and 100 mm. diastolic, the pulse rate 56 a minute and the temperature 98.6 F. (rectal).

Laboratory Findings.—The basal metabolic rate was —36 per cent, the hemoglobin concentration 63 per cent (Sahli), the red cell count 3,740,000 per cubic millimeter, and the white cell count 6,500, with 51 per cent polymorphonuclears.

Course in Hospital.—On numerous occasions the patient felt cold and weak and had a subnormal temperature. The clinical impression was that of endocrine dysfunction, probably on the basis of hypothyroidism. In May 1937 desiccated thyroid, 1 grain (0.065 Gm.) twice a day, was prescribed, and this therapy was continued for ten months. The patient became more alert and responsive and showed greater general activity. Her skin became thin and soft, although it remained somewhat dry. Her basal metabolic rate rose to —2 per cent, but her weight dropped from 98 to 66 pounds (44.5 to 29.9 Kg.) during administration of the thyroid (fig. 1).

The thyroid therapy was discontinued; the basal metabolic rate slowly dropped, and the weight remained approximately at 66 pounds. The patient had recurrent attacks of weakness and hypothermia. Marked dental caries developed. The enamel at the gingiva of nearly all the upper and lower anterior teeth and at the contact points of the upper molars became soft and chalklike, in many places appearing as if dissolved away.

On Oct. 20, 1938 there was a sudden change in her mental condition. She became restless, disturbed, noisy, confused and incontinent and talked loudly and

Fig. 2.—Patient two weeks after the first attack of hypoglycemia. The cachexia, atrophy of the breasts and loss of axillary and pubic hair are readily discernible.

irrationally. About six hours later she became comatose and her pulse weak. Both arms were held extended and overpronated, with resistance to flexion and supination. Both legs were rigidly extended, with the feet plantar flexed. There were bilateral foot clonus and a Babinski sign on the right. There was slight weakness of the right side of the face. Tendon reflexes were markedly exaggerated. The pupils were pinpoint but reacted to light. The eyegrounds were not remarkable.

The blood pressure was 100 mm. systolic and 80 mm. diastolic. The sudden appearance of "decerebrate rigidity" suggested the possibility of cerebral hemorrhage or of uremic or diabetic coma to be differentiated from the hypoglycemia of pituitary cachexia. Specimens of the blood and spinal fluid were obtained for analysis.

The blood sugar was reported to be less than 50 mg. per hundred cubic centimeters. The nonprotein nitrogen of the blood was 42.6 mg. per hundred cubic centimeters. After the intravenous administration of 100 cc. of 50 per cent dextrose, a lumbar puncture revealed bloody spinal fluid containing 98 mg. of total protein and 127 mg. of sugar per hundred cubic centimeters. Intravenous administration of dextrose was followed by dramatic recovery of consciousness and progressive improvement, until the patient again became ambulatory, with complete loss of abnormal neurologic signs. Figure 2 shows the appearance of the patient at this time. One week after this attack of hypoglycemia the spinal fluid was xanthochromic, the total protein 62 mg. per hundred cubic centimeters and the cell count 32 per cubic millimeter, of which 30 were lymphocytes and 2 polymorpho-

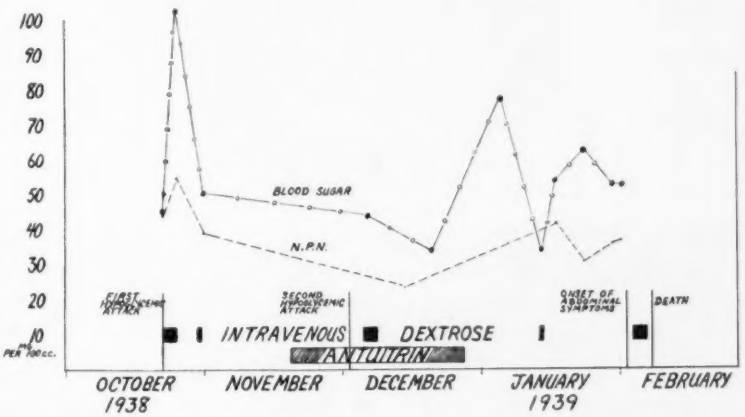

Fig. 3.—Studies on the chemical constituents of the blood following the first clinical hypoglycemic attack. The black blocks represent the days on which dextrose was administered intravenously. The long cross hatched block represents the period throughout which extract of whole anterior lobe of the pituitary (antuitrin) was given (1 cc. twice a week).

nuclears. Gastric analysis revealed complete absence of free hydrochloric acid. Roentgenograms of the skull were noncontributory. The sella turcica was not enlarged.

The diagnosis of Simmonds' disease was made, and extract of the whole anterior lobe of the pituitary (antuitrin), 1 cc. twice a week, was prescribed on Nov. 19, 1938. The patient remained ambulatory, with little or no change, until December 4, when she had another attack of hypoglycemia similar to, although not as severe as, the previous one. She responded well to injections of dextrose and again became ambulatory. She continued to have a subnormal temperature and a slow pulse, and her blood sugar ranged from 33 to 78 mg. per hundred cubic centimeters (fig. 3).

On Feb. 3, 1939 she complained of chills, nausea and pain in the right side of the abdomen. She vomited and had watery stools. Her temperature rose to 103 F. (rectal), her pulse rate to 130 a minute and her white cell count to 13,200 per cubic millimeter, with 76 per cent polymorphonuclears. There was spasm to

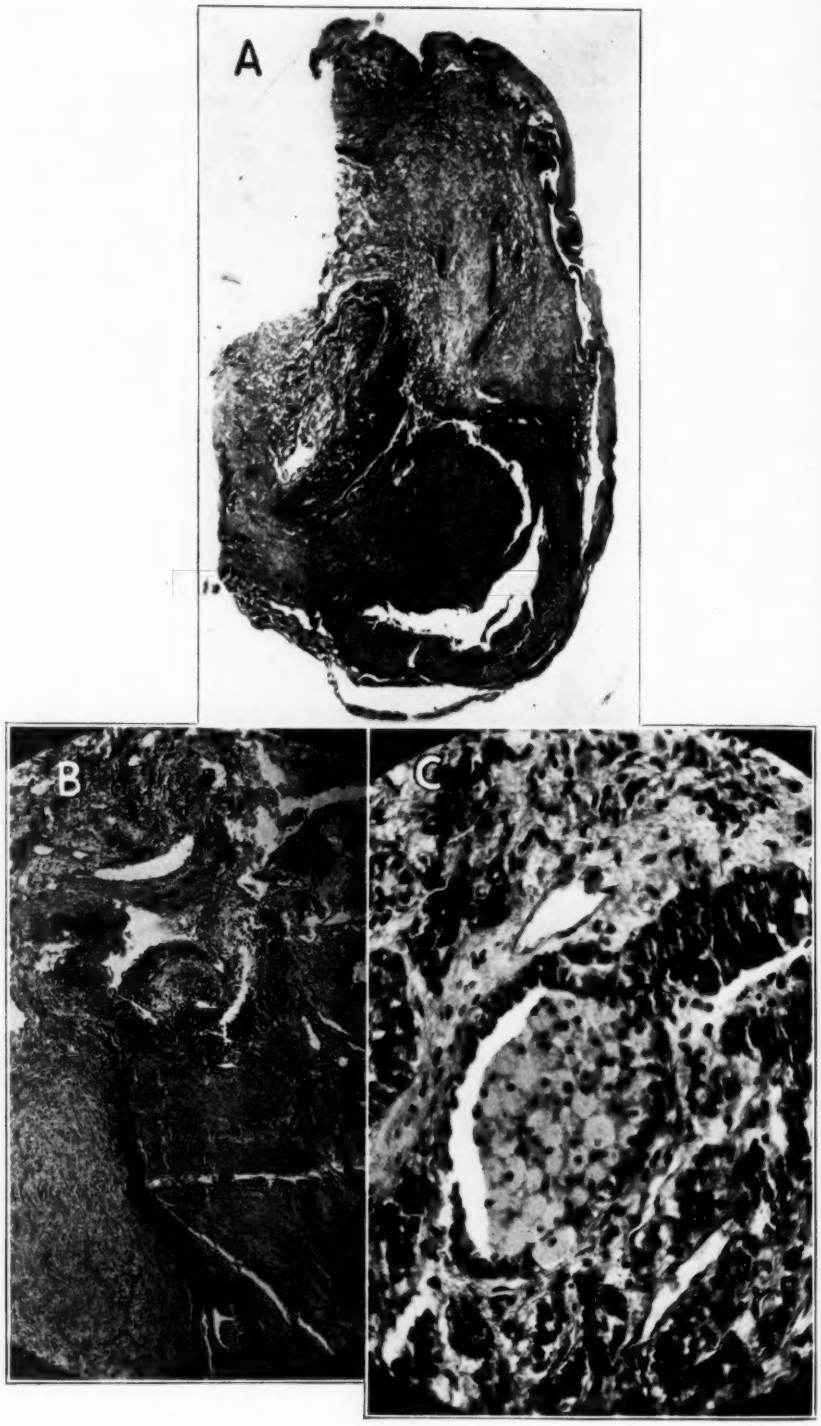

Figure 4

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the right of the umbilicus, with abnormal distention. An exploratory laparotomy revealed a considerable amount of blood-tinged fluid in the peritoneal cavity. Deposition of fibrin was observed along the serosa of the small bowel. The postoperative course was steadily downhill, and the patient died on the fourth postoperative day, at the age of 51.

Autopsy.—Autopsy, performed two and one-half hours post mortem, revealed an emaciated white woman. There was absence of axillary and pubic hair, although the sandy hair of the scalp and eyebrows was essentially unaltered. The teeth revealed considerable dental repair. The skin was dry and shiny. The breasts and external genitalia were extremely atrophic. The abdomen was slightly distended and tympanitic. There was a right rectus incision, extending from 8 cm. above to 8 cm. below the umbilicus. There was an irregular café au lait spot, measuring 3.8 by 1.0 cm., in the right anterior axillary line along the distribution of the ninth thoracic segment. There were several small brownish spots, measuring 0.1 to 0.2 cm. in diameter, over the left instep.

In spite of the apparent emaciation, the subcutaneous fat measured 1.3 cm. over the abdomen and 0.6 cm. over the thorax. The peritoneal cavity contained 125 cc. of fairly clear, slightly blood-tinged fluid. The entire small bowel was moderately distended, and numerous ecchymotic areas were scattered on the serosal surface. There were 75 cc. of clear amber fluid in the left pleural cavity and 125 cc. of a similar fluid in the right pleural cavity. There were dense fibrous adhesions at the right apex. The pericardial sac contained 30 cc. of clear amber fluid. The heart was small, weighing 160 Gm. The foramen ovale was closed. The anterior leaflet of the mitral valve revealed a raised, yellowish atheromatous plaque, measuring 0.4 cm. in diameter. There were a few small, slightly raised, orange-yellow plaques on either side of the aortic ring. The coronary vessels were clear. The lungs revealed scattered patches of early bronchopneumonia, and there was an apical scar in the upper lobe of the right lung. There was moderate congestion of both the serosal and the mucosal surface of the jejunum. The mucosa of the ileum was grayish green. In the upper portion of the ileum were several ulcerative areas, measuring approximately 2 cm. in diameter. The lower portion of the ileum appeared essentially unaltered. The appendix was small and fibrosed. There was a large diverticulum of the transverse colon, which readily admitted 5 fingers. The rest of the colon was essentially unaltered. There was distinct microsplanchnia. The spleen weighed 30 Gm., the pancreas 50 Gm., the liver 570 Gm. and the kidneys together 160 Gm. The uterus, tubes

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EXPLANATION OF FIGURE 4

Fig. 4.—*A*, photomicrographs of the pituitary gland (× 12; Maximow's azure II, and eosin method). The fairly well preserved posterior lobe occupies the lower right-hand corner. Above and to the left can be seen the pars intermedia. The anterior lobe is almost entirely replaced by dense and loose fibrous connective tissue. Dilated vessels can be seen at the periphery of the gland.

B (× 64; hematoxylin and eosin), at the lower left is the posterior lobe. At the lower right is dense scar tissue of the anterior lobe. Just above the center is an area of dense lymphocytic infiltration. At the top is an area of recent hemorrhage and occasional phagocytes containing hemosiderin.

C (× 240; Maximow's azure II and eosin stain), a section through the pars intermedia, showing one acinus filled with and partially lined by large clear cells, with foamy cytoplasm and small, eccentric nuclei.

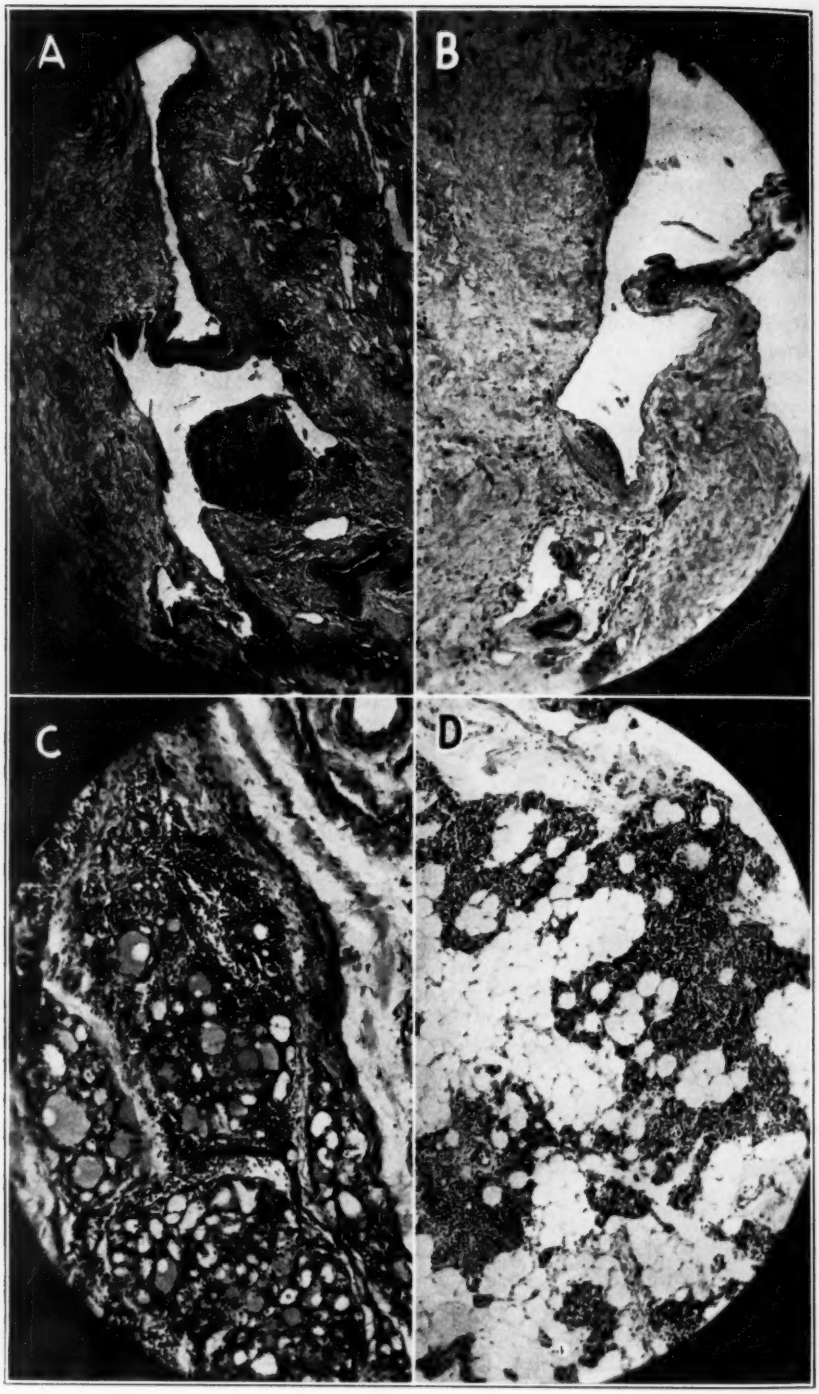

Figure 5

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and ovaries were atrophic. The right adrenal was not found. The left adrenal measured 4.5 by 1.6 by 0.4 cm. The deep orange-yellow cortex measured 0.1 cm. and the medulla 0.2 cm. The aorta revealed numerous small, slightly elevated, atheromatous plaques, which were most pronounced just above the bifurcation of the aorta. The lymph nodes were not remarkable. The bone marrow appeared essentially unaltered. The thyroid gland was not grossly demonstrable (see "Microscopic Examination"). In its usual position there was some dense connective tissue, on which there lay a parathyroid gland, measuring 0.6 by 0.2 by 0.1 cm., and two small lymph nodes.

The dura mater was semitransparent and separated easily from the underlying leptomeninges. The pia-arachnoid was edematous over the parietal and occipital hemispheres. There was moderate congestion of the cortex. The basilar blood vessels were small and collapsed. The pia-arachnoid at the base of the brain was transparent. The cortical convolutional pattern showed no conspicuous abnormalities. The weight of the brain plus the cerebellum was 1,215 Gm. The pituitary gland was unusually small, measuring 0.8 by 0.7 by 0.5 cm. It was firmly adherent to the sella turcica by dense white fibrous adhesions. The pituitary stalk emerged from a grayish umbilicated depression.

Microscopic Examination.—Serial sections were made of the whole pituitary. The anterior lobe was almost completely replaced by dense and loose fibrous connective tissue (fig. 4 *A*), throughout which were scattered areas of recent hemorrhage, numerous large phagocytic cells containing hemosiderin, scattered nests of lymphocytes (fig. 4 *B*), occasional lamellated calcified bodies and a few scattered nests of poorly preserved cells, which appeared to be the chromophobic variety (fig. 4 *A*). Throughout the pars intermedia the epithelial cells were relatively well preserved, with a distinct tendency to acinous formation. There were occasional cysts containing colloid. One acinus was partially lined by and partially filled with large, pale, slightly granular cells with small, peripherally located nuclei (fig. 4 *C*). There were no marked arteriosclerotic changes or any evidence of thrombosis of vessels. However, a striking change was observed in numerous dilated sinusoids, particularly about the periphery of the anterior lobe and, to a less extent, about the periphery of the posterior lobe. There were numerous fibrinoid nodules of varying size, lying immediately beneath the endothelium of these sinuses. Some of these (fig. 5 *A*), apparently of recent development, were fairly homogeneous, slightly granular nodules in which a few poorly preserved

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EXPLANATION OF FIGURE 5

Fig. 5.—*A*, section of the pituitary gland, showing a large subendothelial fibrinoid nodule composed of a fairly homogeneous, slightly granular material, throughout which a few elongated, poorly preserved nuclei are scattered (× 64; hematoxylin and eosin).

B, section of pituitary gland, showing subendothelial lamellated nodules with flattened connective tissue cells in parallel rows (× 64; hematoxylin and eosin).

C, section of thyroid gland, showing atrophic acini surrounded by large numbers of lymphocytes and dense fibrous connective tissue (× 64; hematoxylin and eosin).

D, section of parathyroid gland (× 64; hematoxylin and eosin). The gland is largely replaced by adipose tissue. The remaining parathyroid cells are mostly chief cells.

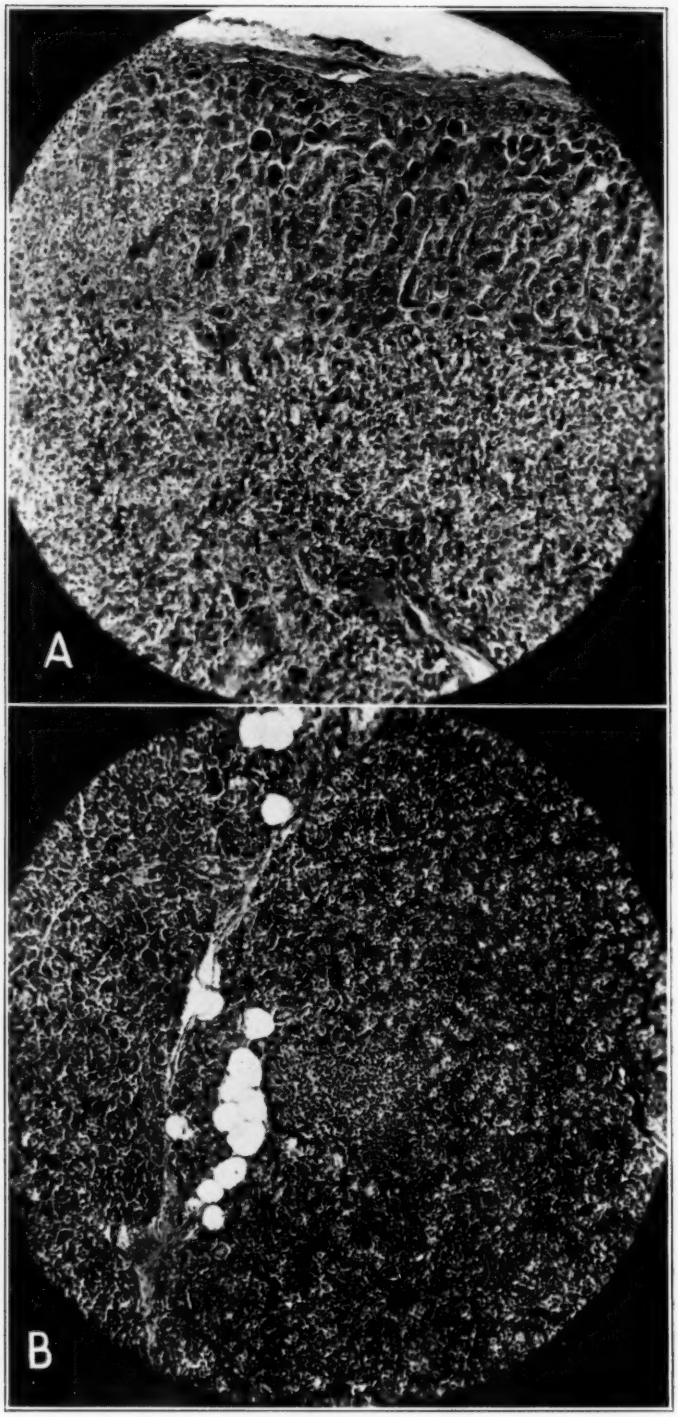

Figure 6

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nuclei could be seen. Other nodules (fig. 5 *B*) appeared somewhat lamellated and contained a few scattered connective tissue cells. There were numerous other subendothelial nodules which appeared to represent intermediate stages. All of them were covered by endothelium. There was little alteration in the posterior lobe except for a small area of dissociation, throughout which was dispersed a moderate amount of coagulated protein.

Most of the thyroid gland was replaced by dense scar tissue. A few small acini were found containing faintly stained colloid and lined by flattened cuboidal epithelium. Large nests of lymphocytes were scattered throughout both the glandular and the scar tissue (fig. 5 *C*).

Approximately one half of the parathyroid gland was composed of fat cells (fig. 5 *D*). The remaining parathyroid cells were, for the most part, chief cells, but an occasional oxyphilic cell was seen. Scattered through the gland between groups of cells were small collections of homogeneous eosinophilic material resembling colloid.

The adrenal cortex was considerably diminished in size (fig. 6 *A*). The zona glomerulosa was only five to six cells in thickness. The zona fasciculata was thin and contained many vacuolated cells. The zona reticularis was hardly discernible. The medulla was essentially unaltered except for a few small nests of lymphocytes.

Throughout the pancreas the islets were numerous, large and contained many nuclei (fig. 6 *B*), although no mitotic figures were seen. They were not sharply demarcated from the surrounding acini, many of which contained a moderate amount of eosinophilic secretion.

The endometrium was atrophic and showed some lymphocytic infiltration. The usual ovarian stroma was largely replaced by dense fibrous connective tissue. Small corpora atretica were found.

The liver and spleen revealed a moderate deposition of hemosiderin. Sections of the myocardium revealed scattered areas of basophilic myxomatous degeneration.

There were marked congestion and edema throughout the sections of the ileum, with scattered areas of hemorrhage. Large phagocytic cells in the mucosa contained hemosiderin. In the mucosa were superficial areas of ulceration containing colonies of coccoid organisms, many of which were grouped in pairs. The entire wall was infiltrated with numerous polymorphonuclears and occasional lymphocytes, plasma cells and large mononuclear cells.

Sections of rib revealed moderate hypoplasia of the bone marrow. Numerous large phagocytic cells contained ingested red blood cells. Scattered throughout the marrow were considerable eosinophilic granular material and scattered faintly staining eosinophilic strands. There were several megakaryocytes with pyknotic

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EXPLANATION OF FIGURE 6

Fig. 6.—*A*, section of adrenal gland (× 64; hematoxylin and eosin). The zona glomerulosa and zona reticularis are particularly atrophic. Vacuolation of the zona fasciculata is seen at the left of the section. Occasional lymphocytes are found in the medulla.

B, section of pancreas (× 64; hematoxylin and eosin). Islets are inconspicuous. The one at the center contains numerous, closely packed cells.

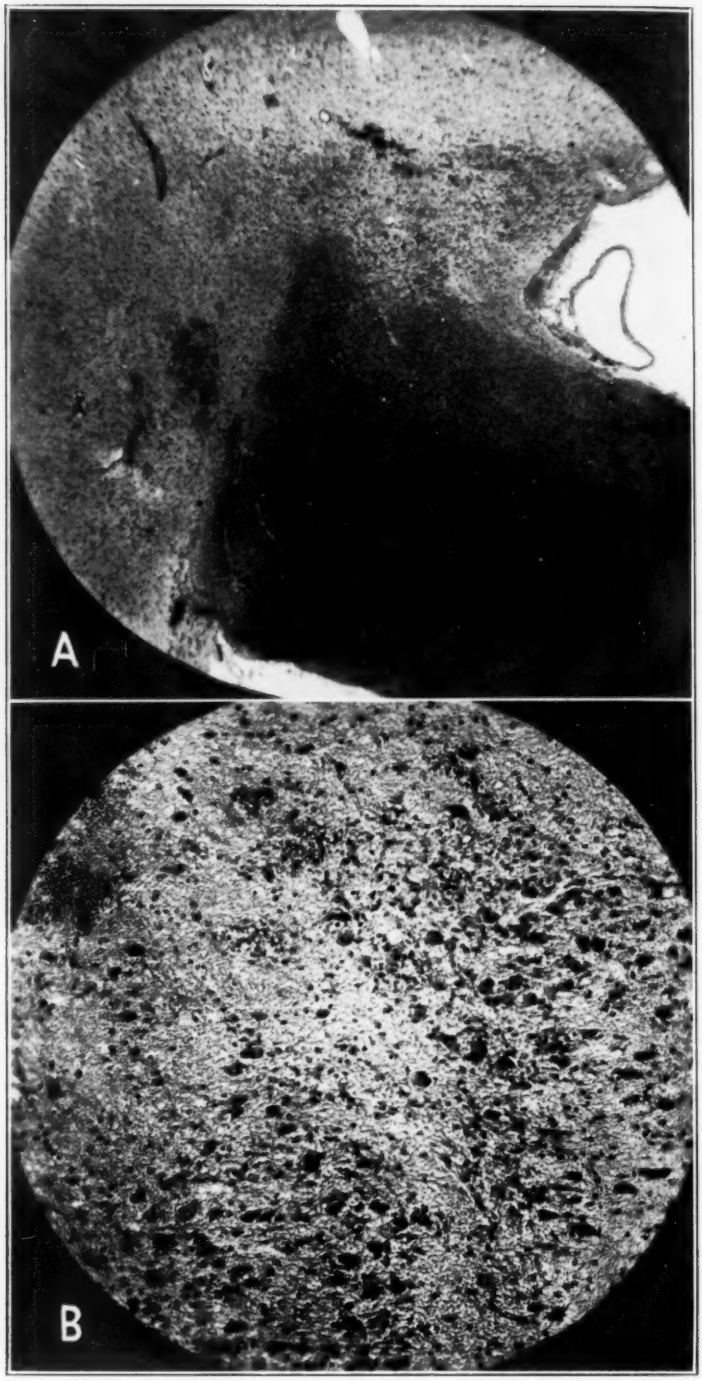

Figure 7

(See legend on opposite page)

nuclei. An excessive amount of fat was present in the marrow. The bony spicules showed no marked osteoporosis.

Sections of the lung revealed healed pneumonitis, with dense scarring and lymphocytic infiltration at the apex and scattered areas of acute bronchopneumonia in the right upper lobe.

Serial pyroxylin sections were made through the hypothalamus and stained by the Weil, Nissl and hematoxylin and eosin methods. Routine sections from other parts of the brain were prepared by these methods, as well as by fat stains and silver impregnation. Scattered irregularly throughout the brain and meninges were small areas of recent hemorrhage. In the meninges and in many of the perivascular spaces were phagocytic cells containing hemosiderin. In many of the perivascular spaces, especially about the vena terminalis, were a moderate number of lymphocytes. There was, however, no thick perivascular "cuffing." Occasional small areas of slight perivascular demyelination were observed, and the perivascular spaces contained occasional phagocytic cells which had taken up lipoid products of degeneration. In the cortex were scattered areas showing "dropping out" of nerve cells with little or no glial response. Smaller similar areas were seen in the cornu ammonis.

Satellitosis of nerve cells was marked in the caudate nucleus and the putamen. In the latter as many as twenty-five could be seen about a single nerve cell. Satellitosis was present to a less marked degree in the thalamus, the red nucleus, the cortex and the posterior hypothalamic nucleus.

Scattered throughout the cortex were occasional cells showing the "chronic cell change" of Nissl. Many such cells were found in the periaqueductal gray matter and some in the lateral hypothalamic area.

In scattered areas throughout the brain recent fibrin thrombi were observed in the small veins. In the substantia nigra there were some loss of pigment from the nerve cells and slight perivascular lymphocytic infiltration. The nerve cells of Meynert's ganglion (nucleus basalis) contained numerous large lipoid granules.

In the supraoptic nuclei there were scattered small areas of recent hemorrhage and areas showing a paucity of nerve cells and an increase in the number of microglia cells (fig. 7 *A* and *B*). The paraventricular nuclei were diminished in size and contained many microglia cells (fig. 8 *A*). There was moderate subependymal gliosis of the third ventricle (fig. 8 *B*).

Anatomic Diagnosis.—The diagnosis was Simmonds' disease, with atrophy of the anterior lobe of the pituitary, thyroid and adrenals; microsplanchnia; secondary degenerative changes in the central nervous system, particularly the hypothalamus; acute enteritis; terminal bronchopneumonia; dilatation of the right side of the heart; pulmonary edema, and bilateral hydrothorax.

EXPLANATION OF FIGURE 7

Fig. 7.—*A*, supraoptic nucleus of the hypothalamus (× 27; hematoxylin and eosin). There is a distinct paucity of neurocytes, with a small area of hemorrhage above the dorsolateral cell group.

B, supraoptic nucleus of the hypothalamus (× 120; hematoxylin and eosin). There are paucity and shrinkage of the neurocytes. Numerous microglia cells are scattered among the neurocytes. Small areas of recent hemorrhage are seen at the upper left.

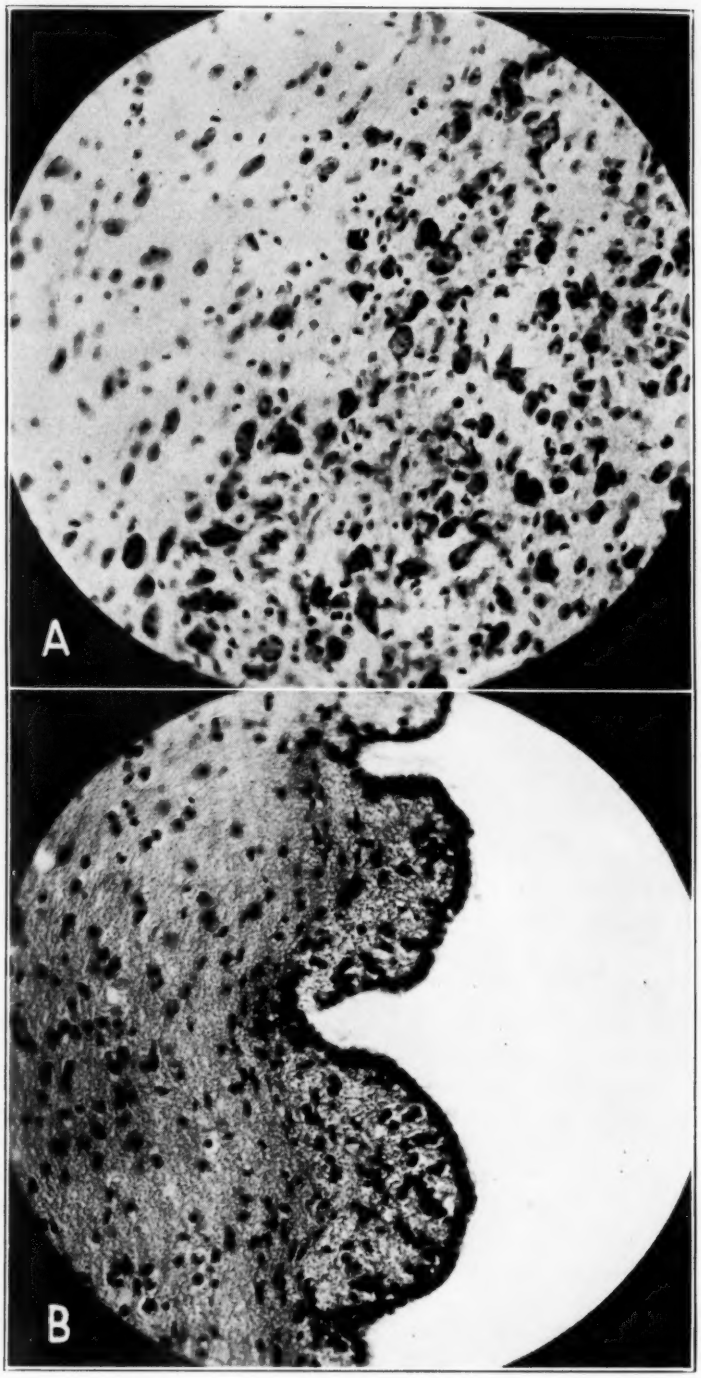

Figure 8

(See legend on opposite page)

COMMENT

Several points in this case are worthy of emphasis, viz., the unusual lesions demonstrated in the pituitary gland, the repeated attacks of hypoglycemia, the presence of a psychosis and the changes in the central nervous system.

Pituitary Lesion.—The lesions found in the dilated sinusoids of the pituitary have not, to our knowledge, been previously described. In some respects they resemble the lesions sometimes seen in cases of rheumatic fever. There were, however, no Aschoff nodules or Aschoff cells, nor were there any gross or microscopic lesions elsewhere in the body suggesting the presence of rheumatic fever. The lesions somewhat resemble the subendothelial hyaline necrosis which one sees in allergic conditions. It is not inconceivable that destruction of the pituitary might occur on the basis of allergic necrosis. The eosinophilia observed in the peripheral blood stream in some cases of Simmonds' disease further suggests the possibility of such a factor. In this case, however, the eosinophil count was never reported to be higher than 2 per cent. In this case, as in many other cases of Simmonds' disease, the clinical course suggests a slowly progressive destructive process. This might be produced by gradual thrombosis of the blood vessels supplying the pituitary, but one would expect to find some morphologic evidence of such a process, which we were unable to demonstrate. The lesions which we have seen, the unique subendothelial fibrinoid nodules and the various stages of fibrosis in the anterior lobe of the pituitary suggest a nonspecific, progressive, destructive, granulomatous lesion, as to the cause of which we are uncertain.

Hypoglycemia.—Attacks of hypoglycemia, even to the point of shock, are not rare in Simmonds' disease. The mechanism which causes them, however, is little understood. The pancreas usually shows little change other than a decrease in size, although some authors have reported an apparent increase in the number of the islets. It is generally accepted that the pituitary gland has a regulatory effect on the blood sugar, but its mode of action is controversial. Houssay and Magenta [12] have shown

12. Houssay, B. A., and Magenta, M. A.: Sensibilidad de los perros hipofisoprivos a la insulina, Rev. Asoc. méd. argent. **37**:389-406, 1924.

EXPLANATION OF FIGURE 8

Fig. 8.—*A*, paraventricular nucleus of the hypothalamus (× 240; cresyl violet). The nucleus is small. The neurocytes are shrunken and diminished in numbers. There is proliferation of microglia cells and astrocytes.

B, lateral wall of the third ventricle (× 240; hematoxylin and eosin). The granularity of the ependymal surface is striking. There is moderate subependymal gliosis.

that the experimental removal of the pituitary gland in dogs results in greatly increased sensitivity to the hypoglycemic action of insulin. Krichesky,[13] in rats, and Adams and Ward,[14] in newts, have demonstrated that removal of the pituitary gland may be followed by an increase in the amount of pancreatic islet tissue. In our patient there appeared to be an increase in the size of the islets and in the number of cells per islet, which may have contributed to the prolonged hypoglycemia which she had. Hypoglycemia is not uncommon in association with Addison's disease. Long and Lukens[15] have shown increased sensitivity to the hypoglycemic action of insulin in diabetic cats the adrenal glands of which had been completely removed. They expressed the belief that the similar results obtained in hypophysectomized animals are dependent on secondary hypofunction of the adrenals.

Although we were at first encouraged by the apparent satisfactory results of thyroid therapy in this patient, the rapid loss of weight caused us considerable apprehension. Castleman and Hertz[16] have emphasized the increased sensitivity of patients with adrenal insufficiency to thyroid extract and have observed precipitation of crises of adrenal insufficiency as a result of its administration to such patients.

Mental Symptoms.—There does not appear to be a uniform mental symptomatology of Simmonds' disease. A review of the varied symptoms reported suggests that a distinction should be made between those symptoms which can reasonably be attributed to pituitary deficiency, including hypoglycemia, and those which appear to be due to a concomitant, unrelated mental illness. Apathy, somnolence, depression and slowing of mental processes might be attributed to the pituitary disease itself. Transient attacks of excited, restless behavior, accompanied by delusions or vivid hallucinations, are very likely due to states of severe hypoglycemia. These hypoglycemic episodes can be dramatically relieved by intravenous administration of dextrose. Grinker[17] has emphasized that the symptom complex in manic-depressive psychosis is identical with the variations of mood accompanying hypothalamic lesions. He cited several cases reported in the literature in which electrical stimula-

13. Krichesky, B.: Relation of Anterior Pituitary to the Volume of Islet Tissue in the Male Rat, Proc. Soc. Exper. Biol. & Med. **34**:126-127, 1936.

14. Adams, A. E., and Ward, E. N.: Effect of Hypophysectomy and of Phyone Injections on the Pancreas and Liver of the Newt, Endocrinology **20**: 496-502, 1936.

15. Long, C. N. H., and Lukens, F. D. W.: The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, J. Exper. Med. **63**:465-490, 1936.

16. Castleman, B., and Hertz, S.: Pituitary Fibrosis with Myxedema, Arch. Path. **27**:69-79 (Jan.) 1939.

17. Grinker, R. R.: Hypothalamic Functions in Psychosomatic Interrelations, Psychosom. Med. **1**:9-47, 1939.

tion of the exposed hypothalamus was performed. Stimulation of the anterior portion of the hypothalamus produced restlessness, excitement, euphoria and mania; stimulation of the posterior portion caused sleepiness and unconsciousness. Foerster and Gagel [18] expressed the belief that cortical functioning is greatly influenced by hypothalamic activity, the cortical functioning being stimulated from the anterior portion and inhibited from the posterior portion of the hypothalamus. However, the fact that, with the present technical equipment, no organic lesion has been demonstrated in most cases of manic-depressive psychosis and the possibility that there may be a complete reversibility of affect force the continued classification of this group in the category of functional psychoses. It is felt that in the case here presented we are dealing with a concomitant manic-depressive psychosis. This conclusion is based on the history of two episodes of depression before the development of Simmonds' disease, which we consider to have been minor attacks of hypomania. We believe that the later episodes of depression were accentuated by the organic disease factor. The two episodes characterized by confusion, restlessness, noisiness, incontinence and subsequent coma we believe were due to the hypoglycemia.

In cases of anorexia nervosa, the physical characteristics of which simulate those of Simmonds' disease, there is usually a fairly characteristic mental picture. In fact, the term anorexia nervosa is really applied to a symptom complex occurring in the setting of a psychoneurosis. In the development of the syndrome there is a complexity of factors, which may be brought out by an analysis of the heredity, personality, physical makeup and environmental situation in the individual case. It is a neurosis with compulsive, obsessive, anxiety and depressive factors, believed by some to be a protection against the assumption of the normal sexual relationship. Although we cannot deny, at present, the possibility of a primary endocrine factor in the pathogenesis of anorexia nervosa, the neurotic factor appears to be outstanding, suggesting that the endocrine factor is secondary. Rahman, Richardson and Ripley [19] and Waller, Kaufman and Deutsch [20] have recently analyzed this type of neurosis. Usually the loss of weight in cases of this condition can be traced to voluntary starvation, which one does not find in cases of Simmonds' disease. The causes of this voluntary starvation are discussed in detail in their reports.

The syndrome of anorexia nervosa is found most frequently in young women, in contrast to Simmonds' disease, which is most apt to appear

18. Foerster and Gagel, cited by Grinker.[17]

19. Rahman, L.; Richardson, H. B., and Ripley, H. S.: Anorexia Nervosa, Psychosom. Med. **1**:335-365, 1939.

20. Waller, J. V.; Kaufman, M. P., and Deutsch, F.: Anorexia Nervosa, Psychosom. Med. **2**:3-16, 1940.

in older women. With the solution of the patient's psychic problems, physical and mental improvement and frequently cure supervene, in contrast to the usual fatal outcome of Simmonds' disease.

Lesions of the Nervous System.—The degenerative changes in the supraoptic and paraventricular nuclei are similar to those described by Gallavan and Steegman [9] and by Kotte and Vonderahe.[10] We believe that these changes are secondary to pathologic changes in the anterior lobe of the pituitary gland. Many of the cell changes, the multiple petechial hemorrhages and possibly the subependymal gliosis may be directly attributed to the repeated attacks of hypoglycemia. We suggest that the terminal ulcerative enteritis may have been initiated by the injury to the hypothalamus, as similar lesions have been reported in human beings and in experimental animals with hypothalamic lesions.

SUMMARY

A case of Simmonds' disease is presented which appeared after childbirth and was associated early in the course of the illness with a manic-depressive psychosis. The pituitary gland showed a unique, progressive, nonspecific granulomatous process resembling allergic necrosis. There was secondary atrophy of the thyroid, adrenals, parathyroids, ovaries, uterus and breasts. These atrophic processes were accompanied by the development of marked cachexia and microsplanchnia. Scattered focal lesions observed in the central nervous system are attributed not to the psychosis but to the repeated attacks of hypoglycemia. Degenerative lesions in the supraoptic and paraventricular nuclei of the hypothalamus are thought to be secondary to destruction of the anterior lobe of the pituitary gland.

DISPLACEMENT AND HERNIATION OF THE HIPPOCAMPAL GYRUS THROUGH THE INCISURA TENTORII

A CLINICOPATHOLOGIC STUDY

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It has long been recognized that a mass lesion within the cranial cavity often produces disturbances of function which cannot be ascribed to the actual site of the growth.[1] One of the causes of "distant" or "false localizing signs" of an expanding intracranial lesion is the shift of the brain substance to produce herniations about certain partially fixed, extracerebral structures and into certain potential spaces within the skull cavity.[2] Thus, a representative herniation, the cerebellar pressure cone, has been understood to have considerable clinical significance ever since it was described by Alquier, in 1905.[3]

Similarly, after Adolf Meyer's description and illustration of herniation of the hippocampal structures into the incisura tentorii,[4] it has become evident that this dislocation of cerebral substance, called by van Gehuchten [5] the "temporal pressure cone," is a consistent producer of secondary functional derangements. Evidence has accumulated to show

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1. Collier, J.: The False Localizing Signs of Intracranial Tumours, Brain **27**:490, 1904.

2. Courville, C. B.: A Study in the Pathological Physiology of Intracranial Neoplasms: The Principle of Transmitted Pressure in the Production of Symptoms, California & West. Med. **29**:2-7 (July) 1928.

3. Alquier, M.: Deux cas d'hétérotopie du cervelet dans le canal rachidien, Rev. neurol. **13**:1117-1118, 1905.

4. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387-400 (Oct.) 1920.

5. van Gehuchten, P.: Le mécanisme de la mort dans certains cas de tumeur cérébrale, Encéphale **32**:113-127 (Sept.-Oct.) 1937.

that such a displaced temporal lobe may cause direct pressure [6] on or indirect vascular changes [7] in the neighboring diencephalon, mesencephalon and rhombencephalon. A clinical picture of the temporal pressure cone has been suggested.[8] This herniation has been offered as the cause of obstructive hydrocephalus,[9] the decerebrate state,[10] anisocoria,[11] ipsilateral disturbances of the pyramidal tract [12] and pseudocerebellar signs [13] in certain cases of a supratentorial expanding lesion. The temporal pressure cone has been incriminated as the cause of death in some cases of tumor of the brain.[14] More recently, investigators have outlined an operative procedure to relieve this dangerous condition and have even suggested that such a procedure might justifiably precede any attempt to remove the intracranial lesion.[15]

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6. Spatz, H., and Stroescu, G. J.: Zur Anatomie und Pathologie der äusseren Liquorräume des Gehirns (Die Zisternenverquellung beim Hirntumor), Nervenarzt **7**:481-497, 1934.

7. Moore, M. T., and Stern, K.: Vascular Lesions in the Brain-Stem and Occipital Lobe Occurring in Association with Brain Tumours, Brain **61**:70-98 (March) 1938.

8. (*a*) Vincent, C., and David, M.: Sur les méningiomes de l'aile du sphénoïde, Cong. internat. de lutte scient. et soc. contre le cancer **1**:700-719, 1933. (*b*) David, M., and Mahoudeau, D.: Les méningiomes de la petite aile du sphénoïde, Gaz. méd. de France **42**:111-131 (Feb.) 1935. (*c*) David, M., and Askénasy, H.: Sur quelques causes d'aggravation rapide et de mort subite dans les syndromes d'hypertension intracranienne, J. belge de neurol. et psychiat. **37**:550-565 (Sept.) 1937; abstracted, Rev. neurol. **68**:918 (Dec.) 1937. (*d*) Le Beau, J.: L'oedème du cerveau. Son rôle dans l'évolution des tumeurs et des abcès intracraniens, Thesis, Paris, 1938; abstracted, Rev. neurol. **69**:295-297 (March) 1938.

9. Smyth, G. C., and Henderson, W. R.: Observations on the Cerebrospinal Fluid Pressure on Simultaneous Ventricular and Lumbar Punctures, J. Neurol. & Psychiat. **1**:226-238 (July) 1938.

10. Jefferson, G.: The Tentorial Pressure Cone, Arch. Neurol. & Psychiat. **40**:857-876 (Nov.) 1938.

11. Reid, W. L., and Cone, W. V.: The Mechanisms of Fixed Dilatation of the Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030-2034 (May 20) 1939.

12. Groeneveld, A., and Schaltenbrand, G.: Ein Fall von Duraendotheliom über der Grosshirnhemisphäre mit einer bemerkenswerten Komplikation; Läsion des gekreuzten Pes pedunculi durch Druck auf den Rand des Tentoriums, Deutsche Ztschr. f. Nervenh. **97**:32-50, 1927. Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274-287 (Feb.) 1929.

13. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behaviour, Life History and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938, pp. 391 and 589.

14. van Gehuchten.[5] David and Askénasy.[8c]

15. David, M.: Les cônes de pression temporal et cérébelleux, cause d'aggravation rapide et de mort subite dans les syndromes d'hypertension intracranienne, Gaz. méd. de France **44**:56-67 (Jan. 15) 1937.

Because of the apparent clinical significance of this type of cerebral herniation and because there has been no study of a large group of cases, it has been attempted in the present investigation to answer the following pertinent questions: What is the frequency of occurrence of the temporal pressure cone? Under what conditions does it develop? What pathologic effects does it have? Is there a group of signs and symptoms produced by this herniation? Can the condition be diagnosed clinically?

MATERIALS AND METHOD

The routine gross examination of all brains in the department of neuropathology of the Neurological Institute of New York has for some years included special observations (under the direction of Dr. Abner Wolf) on the hippocampal, hypothalamic and adjacent regions of the brain stem. When present, the linear indentations ("tentorial grooves") on the orbital surfaces of the hippocampal gyri were measured, the distance being determined from the most medial tip of the uncus laterally to the indentation. This distance was used as a suggestive estimate of the amount of herniation of the hippocampal tissues into the space of Bichat and through the incisura tentorii. The first portion of the investigation concerns the pathologic study from this standpoint of 100 consecutive brains.

The second part of the study is devoted to a clinical analysis of 43 cases selected because of the marked pathologic changes observed in the regions of the hippocampus and brain stem. These cases were studied for possible relations between the pathologic alterations and the signs and symptoms, with the possibility in mind of delimiting a characteristic group of symptoms.

Concluding the study is a clinical and pathologic analysis of a case in which the diagnosis was made ante mortem and which emphasizes the special features of the disturbance in question. The early recognition of this dangerous complication is demonstrated to be as important as it is practical.

PATHOLOGIC STUDY OF ONE HUNDRED BRAINS

The material for the first part of the study was obtained from a consecutive series of brains removed post mortem, from which were excluded only those in certain cases in which the pathologic condition was confined to the structures of the posterior fossa. Deep grooves on the *dorsal* surface of the cerebellar hemispheres were often observed when a tumor involved this structure. Under these circumstances upward protrusions of cerebellar tissue medial to these grooves indicated herniations of the cerebellum through the incisura. On rare occasions we have seen cerebellar grooves of this nature together with marked hippocampal herniations, presumably due to a supratentorial expanding lesion; this

suggests a descent of the tentorial leaves due to pressure from above, with compression of the edges of the incisura on the subjacent cerebellar tissues.

Does the grooving of the hippocampal regions occur in the normal brain? Observations on many brains with no pathologic lesions often revealed the presence of slight tentorial grooves. These grooves were never long and were limited to the uncal portions of the hippocampal gyri. They were always shallow and were never more than 2 to 4 mm. from the tip of either uncus. They were equal in length and depth on the two sides. In the presence of general swelling of the brain grooves

TABLE 1.—*Pathologic Diagnosis of the Lesion in One Hundred Consecutive Brains*

Diagnosis	Number of Cases
Glioblastoma multiforme	37
Astrocytoma	13
Abscess (cerebral, 8 cases); (subdural, 1 case); (extradural, 1 case)	10
Metastatic (carcinoma of lung, 4 cases); (carcinoma of ovary, 1 case); (carcinoma of colon, 1 case); (carcinoma [source unknown], 2 cases); (adrenal neuroblastoma, 1 case)	9
Secondary hydrocephalus (aqueductal stenosis, 2 cases); (arachnoiditis, 1 case)	3
Meningioma	7
Sarcoma of meninges	2
Craniopharyngioma	2
Chromophobe adenoma of pituitary	3
Medulloblastoma	2
Spongioblastoma polare	2
Oligodendroglioma	1
Astroblastoma	1
Chorioepithelioma of pineal gland	1
Schilder's disease	1
Tuberculoma	1
Subdural hematoma	1
Ruptured aneurysm	1
Glioma (unidentified)	2
Ganglioma	1
	100

of this nature tended to be more prominent. It is our feeling that most of these equal, short and shallow grooves were postmortem artefacts.

It may be pointed out here that tentorial grooves on the orbital surfaces on the unci have been observed by us repeatedly in cases of increased intracranial pressure from any cause, such as hydrocephalus, encephalitis, encephalomalacia or cerebral edema. In these cases the herniation was observed invariably to be narrow, short and equal and to present shallow tentorial grooves. The width of the displacement did not exceed 5 mm.

The results of study of 100 brains, as analyzed in table 1, may be summarized as follows:

1. Tentorial grooves were observed in 83 brains. Seventeen showed no such changes.

2. In most of the 17 cases in which no hippocampal changes were observed the lesion was a basal neoplasm (adamantinoma, glioma of the optic nerve, pituitiary adenoma) or a slowly expanding lesion situated far anterior or posterior. Those pituitary adenomas not associated with hippocampal herniations were of the type that grew backward and upward into the interpeduncular space, so that the unci were really lifted up and spread apart.

3. Of the 83 brains in which tentorial grooves were found, 74 showed inequality of grooving as to length, depth and distance from the uncal border. In only 9 brains were the tentorial grooves found to be equal on the two sides.

4. In the 9 brains in which the hippocampal herniations were found to be equal on the two sides, the supratentorial neoplasm occupied a frontal, parasagittal position for the most part. Equal herniations of the hippocampal region occurred most frequently in cases of marked internal hydrocephalus.

5. In the 74 brains in which the hippocampal herniations were unequal on the two sides, measurements of the groove distance from the uncal border have been shown graphically in figure 1. It will be seen that the width of the herniation on one side was often considerable. In 1 case the groove measured 18 mm. from the medial uncal border. This means roughly that the basilar structures in this region were subjected to such stress that there was a shift away from the side of the neoplasm (a right temporal glioblastoma multiforme) to the extent of almost 2 cm. Forty-nine brains showed a one-sided herniation that measured less than 10 mm. In the other 25 brains the herniations measured 10 mm. or more. Bilateral herniations were absent in only 17 cases. In the rest there was a moderate medial shift of hippocampal tissues on the side opposite the maximal herniation. In a few cases this was as much as 6 mm. This is significant, for it indicates that there is operative not only a medial shift on one side but also an opposing force, exerted in the opposite direction, from the other side. This results in a viselike compression of the brain stem. The difference between the degree of herniation on one side and that on the other suggests the actual extent of migration of basilar structures. As can be seen, this shift must often have been considerable.

6. The more marked herniation was ipsilateral to the space-occupying lesion in 56 brains. In 2 brains the herniation was more marked contralaterally. In certain of the brains (16) the lesion was apparently midline or bilateral, yet the herniations were unequal.

7. The length and depth of the tentorial grooves varied considerably. They were greatest in those cases in which the herniations were widest. In cases of the most marked hippocampal herniations, the groove

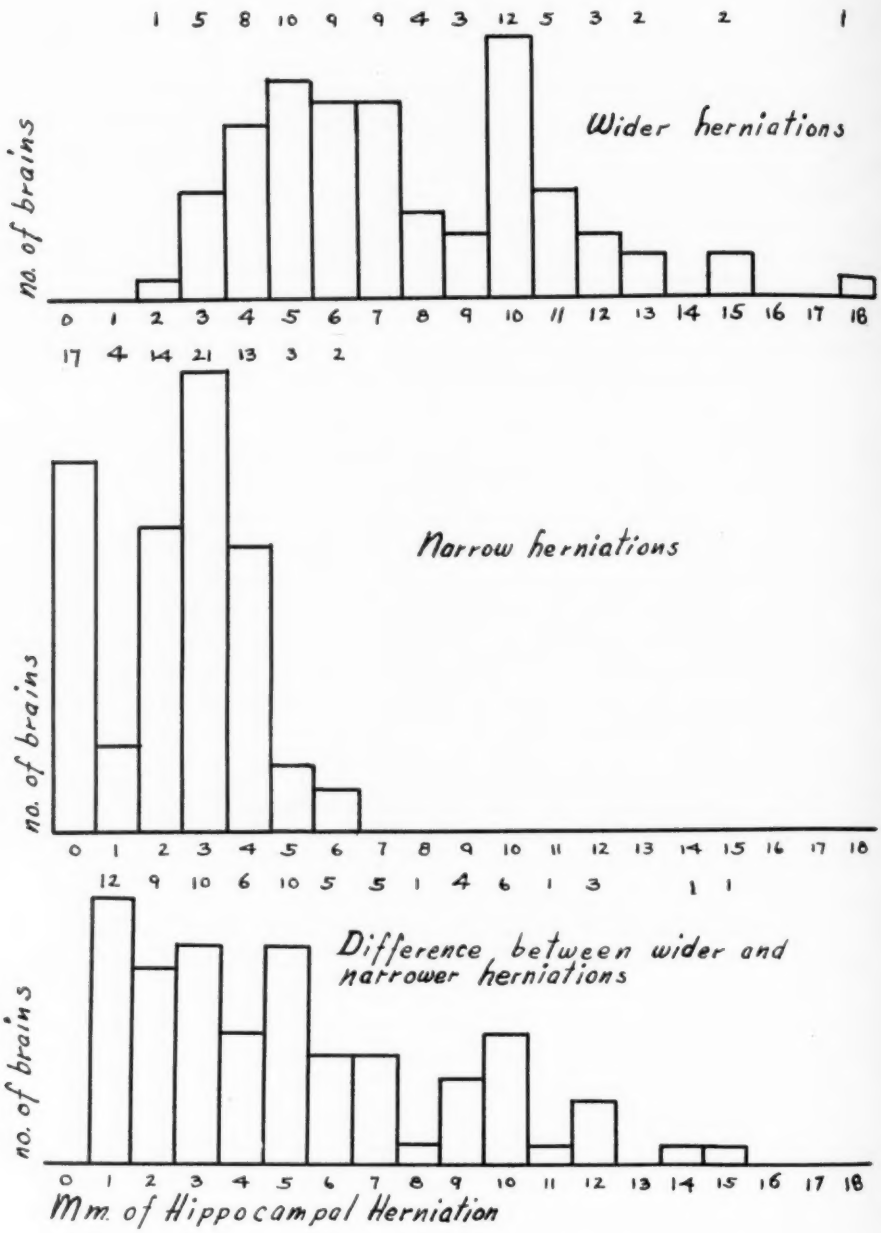

Fig. 1.—Graphs representing the measurements of the distance of the tentorial grooves from the medial aspect of the uncus ("groove distance") in the 74 brains in which displacements and herniations of the hippocampal gyri with supratentorial space-taking lesions were unequal. The uppermost portion shows the distribution of the wider groove distances and the middle part the distribution of the narrower herniations; the lowermost portion represents the difference in each case between the wider and the narrower groove distances, a rough estimate of lateral displacement.

extended back along the orbital surface of the hippocampal gyrus as it surrounds the brain stem and often involved the anteromedial tip of the lingual gyrus, the isthmus of the gyrus fornicatus and the orbital presentation of the gyrus cinguli. At times, apparently when pressure factors directly above the incisura were marked, the splenium of the corpus callosum was also shoved downward into the posterior part of the incisural space. In this manner, a horseshoe-shaped cuff of displaced brain substance came to encircle the brain stem (see figure 5; also Spatz and Stroescu's [6] figures 11, 14 and 15). The grooves were very deep, the vessels and leptomeninges often being carried into them (fig. 8). The herniated tissues were often easily ruptured on removal of the brain at autopsy. Other interesting associated pathologic changes were frequently noted. For instance, we have often observed an apparent

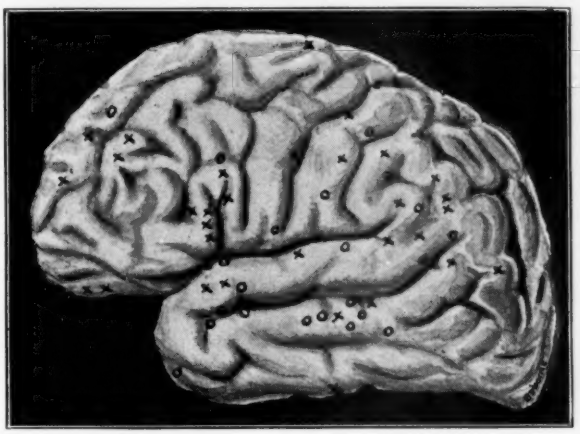

Fig. 2.—Approximate positions of the space-consuming lesions in 58 cases in which one side of the hippocampal herniation presented a groove distance of 5 mm. or more. The positions indicated are merely estimated projections of the apparent center of each lesion. All have been transposed to one side (left) for the sake of compactness, for the sidedness seemed not to have any causal significance. The depth and the exact extent of each lesion could not be clearly shown. Most lesions were deep lying. The marks near the edges of the brain indicate the position of extracerebral lesions. *X* indicates the approximate location of space-taking supratentorial lesion associated with a groove distance of 5 to 10 mm.; *O*, approximate position of expanding supratentorial lesion associated with a groove distance of 10 mm. or more.

widening of the orbital surface of the temporal lobe on the side of the greater herniation (fig. 4). Herniation of the cingulate gyrus (ipsilateral to the expanding mass) beneath the free edge of the falx cerebri was also frequently associated with the more marked temporal pressure cones and indicated the lateral drive produced by the mass lesion.

8. It was noted that the largest herniations occurred in conjunction with glioblastoma multiforme. Cerebral abscess invariably produced marked disturbances in the hippocampal region. Astrocytomas also produced large herniations, but not as consistently as did the glioblastomas. However, it is our impression that the size of the mass lesion, rather than its histologic features, constitutes the more significant factor in producing the temporal pressure cone.

9. Of particular importance in this respect is the position of the supratentorial lesion. In figure 2 are plotted the approximate projected positions of lesions which produced herniations over 5 mm. in width. Expanding lesions in the parietotemporal portion of the brain are most

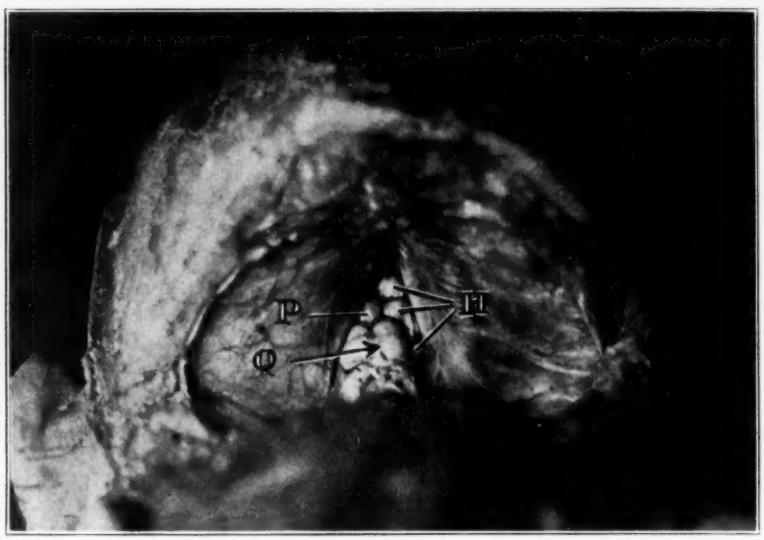

Fig. 3 (see case report).—Hippocampal herniation photographed in situ. The occipital bones and the cerebellum have been removed; the dorsal surface of the brain stem, the incisura tentorii and the cerebellar surface of the tentorium are exposed. Note that the brain stem is shifted to the left. The pineal body (*P*) and the corpora quadrigemina (*Q*) are pushed against the free edge of the left tentorial leaf. The numerous protrusions on the right (*H*) are the herniated portions of the hippocampal gyrus.

liable to produce marked herniation of the hippocampal gyrus, the most marked basilar disturbances accompanying lesions of the temporal lobe. Significant herniations are observed with lesions elsewhere, however, the size of the original focus being the important factor.

10. Grossly, fresh hemorrhages of variable size were found in 19 brains. They were distributed in the following regions: midbrain, 13; pons, 16; hippocampal gyrus, 2; fusiform gyrus, 3, and occipital lobe, 1. Congestion of the blood vessels and parenchymal edema were regularly

noted in the brain stem, the posterior portion of the hypothalamus and the hippocampal gyrus in cases of herniation. The hemorrhages in the fusiform, occipital and hippocampal gyri were invariably on the same side as that of the more marked herniation (figs. 7 and 9). In many brains with marked unilateral or bilateral hippocampal herniations hemorrhages were not apparent grossly, but were seen microscopically. The most severe hemorrhages tended to occur with the largest herniations. In several cases of small, but definite, bilateral herniations,

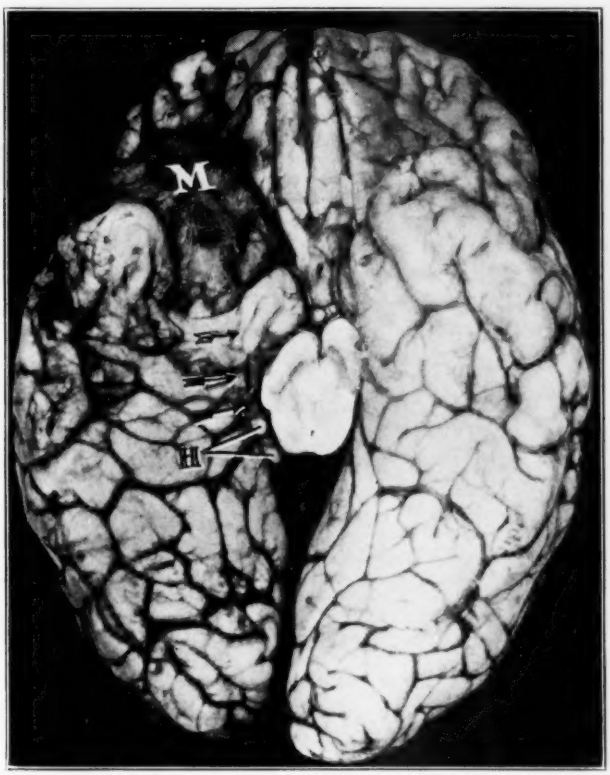

Fig. 4 (see case report).—The large meningioma (*M*) is seen to indent deeply the tip of the right temporal lobe. The tentorial groove is indicated by arrows. The herniated structures seen in figure 3 are seen here as protuberances medial to this groove. There is a slight uncal groove on the left. Note the distortion and displacement of the brain stem, corpora mamillaria and infundibular portion of the hypothalamus.

perivascular hemorrhages of the midbrain and pons, usually associated with an expanding lesion in the temporal lobe, were noted.

11. Representing the remote effects of intracranial mass lesions, distortion, compression, rotation and displacement of the numerous

structures at the base of the brain were noted in 37 brains. These changes were observed to involve the optic chiasm and tracts, the infundibular portion of the hypothalamus, the crura cerebri, the mesencephalon and the pontile portion of the brain stem (figs. 6, 7, 8 and 9). In 29 brains the shift and distortion of these structures were extreme.

In cases of the more marked herniation the tuber cinereum, mamillary bodies and optic tracts were shifted away from the hippocampal hernia-

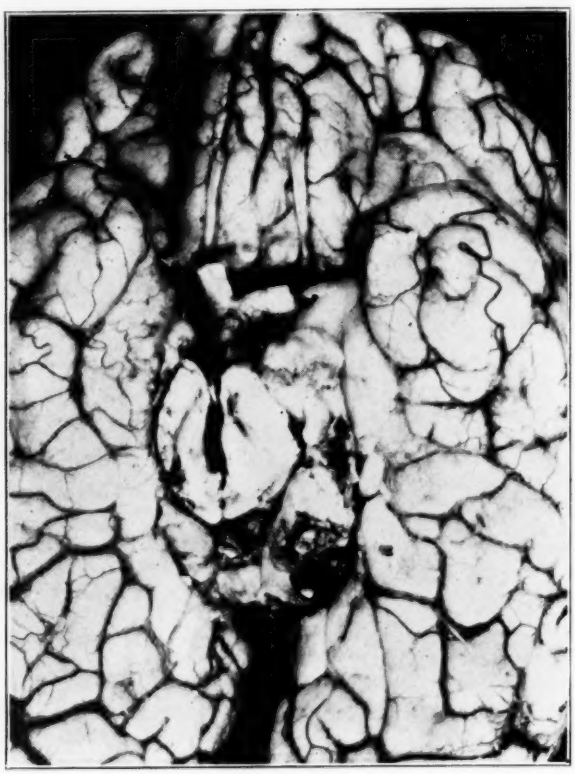

Fig. 5.—Brain of a white woman aged 39. There was an abscess in the posterior portion of the left inferior frontal gyrus, with much edema about it. Note the hemorrhages in the substance of the mesencephalon. The hippocampal herniation is severe and, although extending cufflike about the dorsal portion of the midbrain, is more marked on the left side. The splenium of the corpus callosum has been pushed down to make up the most dorsal part of the herniated mass. The herniated tissues appeared swollen and hemorrhagic and were fragile.

tion and the neoplasm; the midbrain and pons were compressed from side to side, as well as shifted away from the herniated area, and not infrequently rotated away from the region in an apparently ventromedial

direction; the cerebral peduncles were moved contralaterally, distorted and compressed, with the opposite peduncle shoved against the free edge of the other tentorial leaf, and the aqueduct of Sylvius was narrowed, owing to bilateral compression. When the herniations were equal and moderate, but definite, there was no displacement of these structures, but the compression of the mesencephalon narrowed the lumen of the sylvian aqueduct.

12. Of the 100 brains studied, only 22 presented an unequivocal cerebellar pressure cone. Only half of these occurred in brains with a marked temporal pressure cone. The relative infrequency of cerebellar

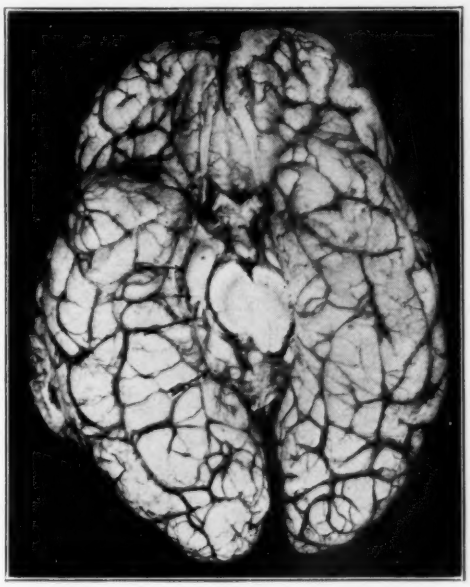

Fig. 6.—Brain of a white man aged 38. The lesion was a polar spongioblastoma of the right parietal lobe and the adjacent frontal and temporal lobes and thalamus. Note the deep tentorial groove on the right with the herniated hippocampal gyrus medial to it. The pia-arachnoid has been stripped from the right uncus. Only a slight left uncal groove is present. The brain stem is greatly distorted and displaced toward the left. The mamillary and infundibular regions also share in the shift to the left. The aqueduct of Sylvius is collapsed.

herniation in our series suggested the relative unimportance of this disturbance in cases of a supratentorial lesion as compared with the temporal pressure cone.

13. In 57 brains the lateral ventricles, the third ventricle and/or the aqueduct of Sylvius were dilated. Two brains had not been sec-

tioned, so that the state of the ventricular structures was not known. In 22 brains obvious obstruction by the primary lesion somewhere along the ventricular pathway seemed to have produced the observed dilatation. In the remaining 35 brains the dilated lateral and third ventricles obtained in the absence of definite obstructive factors. Concurrent with the dilatation in the majority of these cases were large hippocampal herniations.

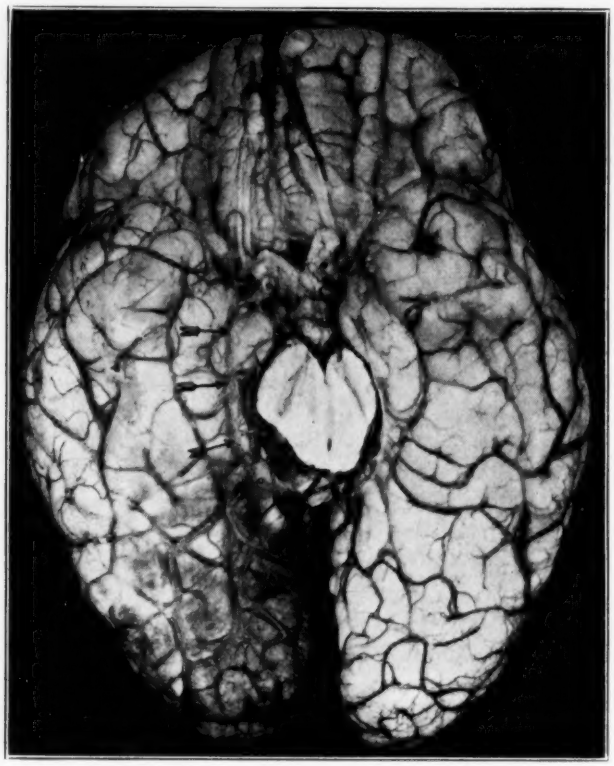

Fig. 7.—Brain of a white woman aged 63. There was a large glioblastoma multiforme in the centrum semiovale of the right parietal lobe. Note the tentorial groove extending along the right hippocampal gyrus. The discoloration of the right occipital lobe and the posterior portions of the fusiform and hippocampal gyri was found to be due to innumerable small cortical hemorrhages. Note that the hemorrhagic area is distal to the tentorial groove. Again, there is distortion of the brain stem and hypothalamic region.

CLINICAL CONSIDERATIONS

With respect to the clinical aspects of hippocampal herniation, the case material was analyzed with the following points in mind: (*a*) Were certain signs and symptoms described by some observers as characteristic

of the temporal pressure cone featured in our cases? (*b*) Were there any clinical features of particular diagnostic significance? (*c*) To what degree is the hippocampal herniation responsible for false localizing or "distant" signs and symptoms?

TABLE 2.—*Preoperative Clinical Analysis*

	Pathologic Series (Tentorial Herniations), Number of Cases (43)	Control Series (No Tentorial Herniations), Number of Cases (21)
Subjective (symptoms)		
(a) Occipitally radiating headache	7	4
(b) Olfactory hallucinations	5	0
Objective (signs)		
(a) State of consciousness		
(1) Coma	2	0
(2) Stupor	9	2
(3) Drowsiness	9	3
(b) Alternating states of coma and consciousness	5	0
(c) Stiff neck	16	6
(d) "Decerebrate rigidity"	6	0
(e) Respiratory disturbances	6	0
(f) Cardiovascular disturbances	8	0
(g) Uncontrollable hiccups	1	0
(h) Pyramidal tract signs		
(1) Contralateral to cerebral lesion	32	12
(2) Ipsilateral to cerebral lesion	4	0
(3) Side alternating	6	0
(4) With flaccidity	8	3
(i) Imbalance of extraocular muscles	13	1
(j) Pupillary disturbances		
(1) Anisocoria	18	2
(2) Pathologic reflex reactions	14	0
(3) Dilated pupil ipsilateral to cerebral lesion	9	1
(4) Dilated pupil contralateral to cerebral lesion	9	0
(5) Side alternating	2	0
(k) Respirations failed before heart action	14	0
(l) Temperature abnormalities	10	1

TABLE 3.—*Postoperative Clinical Analysis*

	Pathologic Series, Number of Cases (43)	Control Series, Number of Cases (21)
Pyramidal tract signs		
(a) Shifted to opposite side	3	0
(b) Sudden alterations	6	0
Marked respiratory difficulties	21	0
Marked cardiovascular difficulties	16	4
Marked temperature abnormalities	14	2
Profuse perspiration	4	0

Tables 2 and 3 were compiled from detailed clinical and postmortem studies of 43 cases of a supratentorial expanding lesion in which the hippocampal herniations were most pronounced, and of 21 selected control cases of a similarly situated lesion in which no herniations were

present.[16] In thus contrasting the clinical features of two series of cases differing only with respect to this particular pathoanatomic feature, it becomes apparent that certain definite signs and symptoms recur with great frequency in the presence of hippocampal herniation.

1. Of the subjective complaints recorded in the 43 cases of the pathologic series, occipitally radiating headache was featured in 7 instances and olfactory hallucinations in 5; in the control series, occipitally radiating headache was present in 4 cases. Olfactory hallucinations, when present, were usually an inconstant complaint. In 1 instance, déjà vue phenomena were a consistent accompaniment of the hallucinatory episodes.

2. Outstanding among the objective signs in the pathologic series were: (*a*) paradoxic signs of involvement of the pyramidal tract; (*b*) "decerebrate rigidity"; (*c*) imbalances in extraocular muscles; (*d*) pupillary dysfunction; (*e*) marked alterations of the state of consciousness; (*f*) cardiovascular and respiratory disturbances, and (*g*) heat-regulatory disturbances. These manifestations were significantly rare in the control series.

3. Stiff neck proved to be a relatively common complaint in both the pathologic and the control series. It was discovered in 16 of the 43 cases of the pathologic series and in 6 of 21 cases of the control series.

4. In 6 cases pyramidal tract signs were demonstrated to have shifted to the opposite side at least once during the preoperative period. In 8 instances a marked degree of flaccidity prevailed in the presence of hyperreflexia and other classic signs of disease of the pyramidal tract. For the most part, alterations in muscle tone and in the laterality of pyramidal tract signs followed interference with the intracranial pressure balance

16. Early in the course of tabulation the necessity for a carefully selected control series became apparent. It was obvious, for example, that the strikingly high incidence of anisocoria in cases of marked hippocampal herniation could not be interpreted unqualifiedly on the basis of cause and effect until, by careful elimination, all extraneous factors bearing on the production of unequal pupils were fully eliminated in the selection of the control series. Thus were excluded in the selection of this series all cases of tumor of the midbrain, pituitary adenoma, intraventricular hemorrhage, lesions of the posterior fossa, basal meningitis, abscess of the pons or midbrain, suprasellar lesions, and the like. Only cases in which the brain bore no trace of tentorial grooves or hippocampal herniations were qualified. When the high incidence of tentorial grooves in any series of brains is taken into account (83 of 100 brains in the present instance), the limitations imposed on the selection of a control series become especially manifest. This explains why the control series (in which there were no tentorial grooves) included only 21 cases of supratentorial mass lesions. The control material consisted of cases of supratentorial expanding lesions similar to those of the pathologic series, differing only in not having an associated temporal pressure cone.

by lumbar puncture, encephalographic or ventriculographic examination or craniotomy.

5. Also greatly influenced by measures affecting intracranial pressure equilibrium was the occurrence of "decerebrate phenomena." These signs invariably presaged death. Attacks of "decerebrate rigidity," usually with demonstrable Magnus-de Kleyn reactions, were recorded in 6 cases. In every instance during the course of these attacks, pupillary and cardiorespiratory abnormalities occurred.

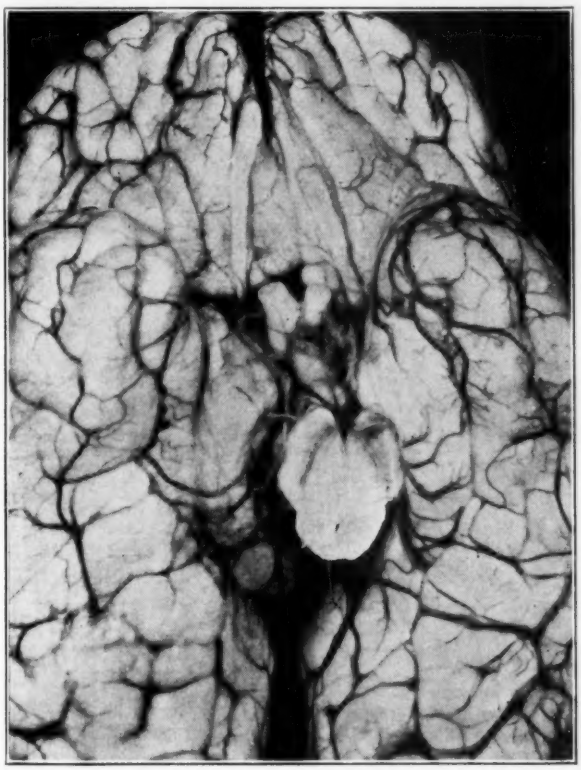

Fig. 8.—Brain of a white man aged 39. A large glioblastoma multiforme occupied the right temporal lobe. Note the deep tentorial groove on the right with markedly herniated hippocampal tissue. The brain stem is compressed from side to side, as well as displaced toward the left. The mamillary and infundibular portions of the hypothalamus and optic chiasm are also shifted markedly toward the left. There is only a slight tentorial groove on the left side.

6. Among the most prevalent of all signs in this series were those referable to movements of the eyeballs. Aside from palsies of the rectus externus muscle there were 13 cases in which mixed oculomotor dys-

function was exhibited. Included in this category are 4 cases in which limitation of upward gaze was present.

7. Abnormalities of pupillary functions were also common. Anisocoria was described in 18 cases. In the control series this was present in only 2 of 21 cases. The dilated pupil was found on the side of the lesion in 9 cases. The size and reactivity of the unequal pupils varied considerably from time to time. Also subject to sudden alterations were

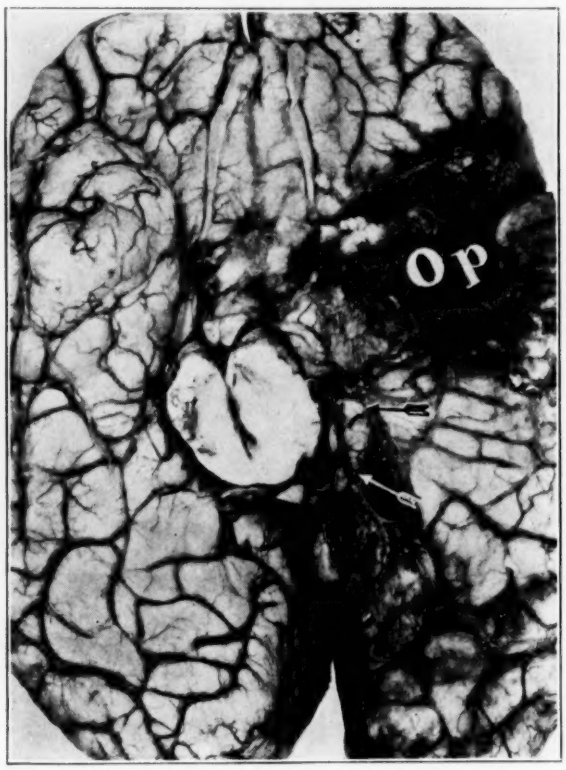

Fig. 9.—Brain of a white man aged 53. There was a large astrocytoma in the left temporal lobe. The discolored area (*Op*) is the operative site. Note the marked tentorial groove outlined by arrows on the left hippocampal gyrus. The dusky appearance of the left occipital, fusiform and hippocampal gyri proved to be due to a hemorrhagic infarct in this area. Note the distortion, displacement and rotation of the mesencephalon. The aqueduct of Sylvius presents a typical narrowing.

the pupillary reactions, marked disturbances of the light reflex being shown at one time or another throughout the clinical course in 14 cases. To a lesser degree, this was also true of the accommodation reaction of the pupils.

8. In 5 cases unconsciousness, sudden in onset, without convulsions, was one of the complaints on admission. Marked alterations in the state of consciousness proved to be an outstanding feature in the pathologic series. These changes were apt to be sudden and dramatic. Profound coma was likely to prevail at any time either before or after operation. This alarming situation usually followed any procedure that tended to interfere with the balance of intracranial pressure. Often occurring simultaneously with these aberrations in the state of consciousness were other physical signs indicative of midbrain embarrassment. Despite recurrent episodes of this nature, during which vital functions appeared seriously compromised, the periods between attacks were often singularly free of any sign of impending danger.

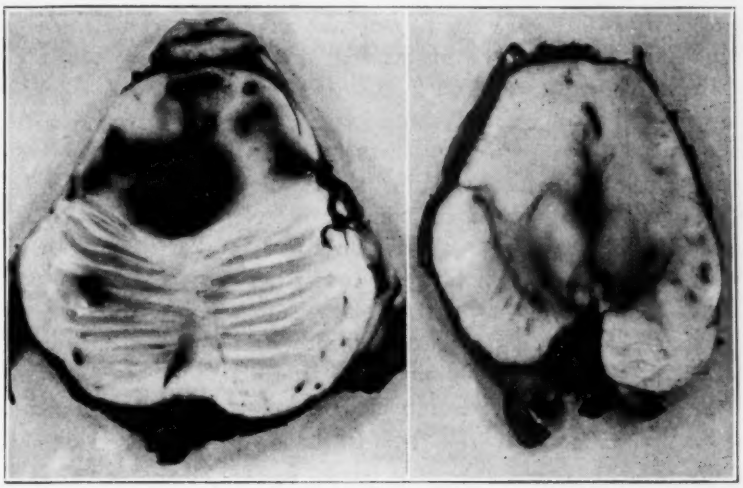

Fig. 10.—The cut section of the pons shows the numerous hemorrhages in the tegmentum and basis. The cut surface of the mesencephalon shows a rather diffuse hemorrhage about the red nuclei and in the midline. The aqueductal flattening and narrowing are well shown here.

9. On admission to the hospital, 6 patients with a temporal pressure cone exhibited outstanding evidence of respiratory embarrassment. The abnormalities of respiration were rarely constant features in each case, and varied in degree from time to time. Cheyne-Stokes, "forced draft" or Biot respirations occurred in these cases. Sudden alterations in the character and rate of the pulse were common. Frequent extrasystoles were described in 1 case.

10. Both the pulse and the respiration were markedly susceptible to any surgical procedure. In 21 cases in which operation was performed alarming respiratory sequelae, such as periodic apnea, hyperpnea or

Cheyne-Stokes respiration, were displayed. In the absence of any operative procedure, there was "respiratory death," i. e., sudden failure of respiration before cessation of the heart beat, in 14 cases.

11. In 24 cases pronounced thermoregulatory disturbances occurred. In none of these cases could the rise in temperature be satisfactorily explained by factors other than the intracranial situation. In 10 of the cases, independent of any operative intervention, there were significant elevations in temperature in conjunction with respiratory irregularities. In 7 of these 10 cases the temperatures ranged from 104 to 106 F. The clinical course was usually stormy and was characterized by periodic aberrations in the state of consciousness and marked respiratory difficulties. They resulted in "respiratory death" whether or not the patient was subjected to surgical intervention. In 4 cases no operation was ever performed and the patient was never subjected to any procedure which disturbed the intracranial pressure balance; yet in these cases high temperatures (104 F. or over) developed and followed a course in every respect like those in the postoperative cases. In 14 cases similar thermoregulatory disturbances appeared postoperatively. It is noteworthy that these signs usually developed shortly after surgical intervention (lumbar puncture and encephalographic examination are included in this category). After such intervention the rise in temperature was usually high, ranging from 103.5 to 109 F. The rise in temperature was usually a prelude to respiratory failure. In evaluating the temperature curves in the cases in which thermoregulatory disturbances occurred, it was difficult to determine to what extent they were modified by procedures intended to lower the body temperature.

Eight patients were reported to have had profuse, drenching perspiration. This sign was accompanied in every instance by thermal and respiratory abnormalities.

12. The signs as described in the preceding paragraphs often dominated the clinical picture after any procedure which upset the pressure equilibrium in the cranial cavity. Once the cardiorespiratory and thermal disturbances became evident (and this is also true of the other signs discussed), the usual procedures designed to reduce intracranial pressure or to support failing vital functions had only temporary beneficial effects.

COMMENT

It may be questioned whether the signs and symptoms which occur in the presence of hippocampal displacement are due to the general, nonspecific effect of increased intracranial pressure. Regarding this, it must be pointed out that the degree of intracranial hypertension was often as great in our cases in which there was no hippocampal herniation as in those in which this dislocation was evident. Furthermore, Browder

and Meyers [17] have raised the intracranial pressure in human subjects to heights (110 mm. of mercury) seldom seen in patients with cerebral neoplasm without producing untoward changes in the pulse rate, blood pressure or state of consciousness. It is our opinion that intracranial hypertension per se was not directly responsible for these changes.

We have noted a considerable fluctuation in the size of the pupils from time to time, probably depending on varying pressure factors within the region of the mesencephalon. However, it may be that the pupillary disturbances are not of central origin, for Reid and Cone [11] have provided a careful experimental basis for the peripheral genesis of anisocoria. It is possible that the oculomotor nerve in its intracranial course is pressed on as well as stretched by the herniated hippocampal tissue or the displaced basilar structures. The anisocoria may be ipsilateral or contralateral to the herniation and the lesion. Therefore, anisocoria may have little localizing value. Reflex pupillary disturbances also vary considerably, but when they occur late are an unfavorable sign. Ptosis may also result, although it may be overlooked when other more grave events are occurring.

Nuchal rigidity is an important sign. It is not consistently associated with pain and is not accompanied by the Kernig or the Brudzinski sign. It may occur late in the clinical course, often postoperatively. It may be associated with an abnormal position of the head and resistance to lateral movements of the head on the neck. The position of the head in such cases may be due to pressure on and distortion of the quadrigeminal plate (Ferrier [18]). Paralysis of upward gaze, as described in our cases, is probably a related factor.

Certain signs and symptoms of involvement of the pyramidal tract are apparently associated with hippocampal herniation. When the expanding intracranial lesion producing the herniation does not involve the motor radiations, pressure by the herniated hippocampal tissue on the ipsilateral cerebral peduncle may produce contralateral upper motor neuron disturbances. Likewise, the shift of the brain stem away from the herniation may cause the contralateral crus to press against the free edge of the contralateral tentorial leaf.[12] This results in an upper motor neuron disturbance ipsilateral to the hippocampal herniation and the lesion. The two mechanisms operating together may give rise to bilateral pyramidal tract signs.

The excessive tone of the extremities and the variations of tone with changes in the position of the extremities were observed several

17. Browder, J., and Meyers, R.: Behavior of the Systemic Blood Pressure, Pulse Rate and Spinal Fluid Pressure Associated with Acute Changes in Intracranial Pressure Artificially Produced, Arch. Surg. **36**:1-19 (Jan.) 1938.

18. Ferrier, D.: The Functions of the Brain, London, Smith, Elder & Co., 1876, chap. 15; New York, G. P. Putnam's Sons, 1876.

times. Jefferson [10] represented this as the "decerebrate state" in man. It appears that physiologic decortication may occur either as a consequence of direct mechanical compression of the brain stem or as a result of intra-axial hemorrhage of the midbrain, both of which pathologic complications are amply demonstrated in these cases.

Hemorrhages, which are to be found in the hippocampal fusiform and occipital gyri, as well as in the brain stem, are of considerable pathologic interest. We are in full accord with Moore and Stern [7] in presuming that the hemorrhages in these two areas are of different origin. Hemorrhages in the temporal and occipital cortex are multiple and pinpoint and present the microscopic pattern seen in hemorrhagic infarction of the cerebral cortex. It is believed that they are produced by compression by the temporal pressure cone on the posterior cerebral arteries and veins. The pontomesencephalic hemorrhages are more difficult to explain. Moore and Stern [7] have pointed out that pathologically they resemble those seen in cases of hypertensive apoplexy. The production of hemorrhages in this location by experimental methods [19] offers a means of investigating further this interesting problem.

The occurrence of an enlarged lateral ventricle contralateral to the supratentorial expanding lesion and of an enlarged third ventricle was not an unusual observation in brains with herniation. With the lateral displacement of the brain stem or its bilateral compression by the herniated hippocampal tissue, we have repeatedly noted flattening of the aqueduct of Sylvius. It is possible that herniation of the hippocampal gyrus may thereby operate as a causative factor in the production of obstructive hydrocephalus.

The changes described in the midbrain and the hypothalamic region may be causally related to a group of signs and symptoms which we have included under the head of "neurovegetative" disturbances. Fluctuating changes of consciousness and hypersomnolent states are often seen in patients with herniation. The investigations of Hess,[20] Ranson [21] and others have shown that the posterior hypothalamic region

19. Dill, L. V., and Isenhour, C. E.: Etiologic Factors in Experimentally Produced Pontile Hemorrhages, Arch. Neurol. & Psychiat. **41**:1146-1152 (June) 1939.

20. Hess, W. R.: The Autonomic Nervous System, Lancet **2**:1199-1201 (Dec. 3) 1932; Hypothalamus und die Zentren des autonomen Nervensystems: Physiologie, Arch. f. Psychiat. **104**:548-557, 1936.

21. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1-23 (Jan.) 1939. Ingram, W. R.; Barris, R. W., and Ranson, S. W.: Catalepsy: An Experimental Study, ibid. **35**:1175-1197 (June) 1936. Ranson, S. W.: Some Functions of the Hypothalamus: Harvey Lecture, Dec. 17, 1936, Bull. New York Acad. Med. **13**:241-271 (May) 1937; in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 92.

is concerned with sleep and the waking state. Evidence has also been accumulated to show that the hypothalamic region contains the head nuclei for respiratory and cardiac control. Cardiorespiratory difficulties in these patients may be due either to direct involvement of these structures in the hypothalamus or to lesions in the pathways connecting these structures with pontomedullary centers as they pass through the midbrain and upper part of the pons. Again, these effects may be due to direct mechanical factors or to secondary results of vascular compression or occlusion. The occurrence of periarterial hemorrhage and venous congestion supports the latter view.

Sudden cessation of respiration with the development of a rapid, bounding, often irregular pulse occurs frequently in these patients. The pulse may continue for a long time if respiration is maintained artificially. This has always been considered to be a "medullary death." However, it is suggested that the temporal pressure cone may be responsible for this to a considerable extent by interrupting or disturbing the cardiorespiratory pathways at a higher level, between the diencephalic and the pontomedullary centers. In many of our cases a tendency to a rise in temperature, a rapid, irregular pulse and hastened, labored respiration have been exhibited. Erickson [22] has grouped these signs together as a definite clinical entity, which he has called "neurogenic fever." Such a syndrome might well result when hippocampal herniation disturbs the structure and blood supply of the hypothalamus, in which thermoregulatory centers have been found, and of the midbrain, through which respiratory and cardioregulatory fibers pass from the autonomic nuclei to the medullary centers.

We feel that when herniation of the hippocampal gyrus occurs in the presence of a supratentorial expanding lesion the prognosis must be altered in any given case. It may mean "sudden death." When this dangerous complication occurs it is important that no measures be instituted that might further aggravate an already unbalanced transtentorial situation.

REPORT OF A CASE

History.—A. R., a white woman aged 43, was admitted to the Neurological Institute of New York on April 16, 1938. Frequent, mild headaches, located chiefly on the top of her head, had begun three years before admission. Early in 1937 the patient had transient diplopia, which lasted about four months. She complained of blurred vision, worse in the right eye, early in the summer of 1937. The reduction in vision was slowly progressive thereafter, so that about two months preceding admission to the hospital the patient could no longer read. On admission she could barely see. For six months she had noted a "pins and needles," or "electrical," sensation in the right side of her face, starting in the

22. Erickson, T. C.: Neurogenic Hyperthermia (A Clinical Syndrome and Its Treatment), Brain **62**:172-190 (June) 1939.

lower portion and spreading upward gradually to involve the eyelids and the frontal portion of the scalp on the right. About once in two weeks, for three months, the patient had had "dizzy spells" for short periods. There were brief episodes of weakness during which she suddenly collapsed without losing consciousness and exhibited convulsive movements, from which she readily recovered in a few moments. On April 1, 1938 the patient became comatose, but slowly recovered. During this comatose state she is stated to have had paralysis of the left upper extremity. Some weakness of the left upper extremity persisted after she regained consciousness. There was marked impairment of memory following this episode. For a year she had diminished sense of smell bilaterally.

Examination.—There were some evidence of generalized loss in weight, definite pyorrhea alveolaris and a pustular eruption on her forehead. Supported, she could walk only with unsteady, short steps. Her neck was stiff and her head fixed. Passive movements of her head were resisted, with complaint of pain. There was a change of tonus of the extremities with passive movements of the head. When the face was turned forcibly to the right, there were flexion of the ipsilateral lower extremity and, less regularly, flexion of the ipsilateral upper extremity. When the head was turned to the left, the left extremities did likewise. The Kernig and Lasègue signs were absent. Paresis of the left upper extremity was more marked in the proximal muscle groups. There was marked hypertonicity of the arm and shoulder muscles on the left side. She used her right hand poorly for skilled acts. Speech was often slurred. The deep reflexes were equal and active on the two sides. The Babinski and Chaddock signs were questionable on the right, but a definite tibial sign of Strümpell was demonstrated bilaterally. No sensory changes were noted. Olfactory sense was reduced bilaterally. Vision was 20/50 —2 in the right eye; she barely saw moving objects with the left. The presence of left homonymous hemianopia was strongly suspected. Papilledema measured 2 D. bilaterally. There was considerable secondary optic atrophy. The right pupil was slightly smaller than the left. The light reaction was good in the right pupil and absent in the left. There was slight external strabismus, with suggestion of exophthalmos bilaterally. She could not converge her eyes. There was palsy of the left facial nerve of central type. The patient showed considerable emotional instability, with depression and anxiety predominating. She was poorly cooperative, because of easy distractibility. The presence of a hippocampal herniation was suspected as a complicating factor.

Laboratory Data.—The blood count was normal. The erythrocyte sedimentation rate was 18 mm. per hour. The results of urinalysis were essentially normal. Routine chemical determinations on the blood were normal. The Wassermann reaction of the blood was negative. Examination of the cerebrospinal fluid revealed 2 white cells per cubic millimeter, a 3 plus reaction for globulin, 160 mg. of protein per hundred cubic centimeters, a colloidal gold curve of 1111122100 and a negative Wassermann reaction. A roentgenogram of the skull showed that the dorsum sellae was atrophic. The pineal gland was calcified, seemed to be displaced to the left and was depressed. These observations suggested an intracranial tumor on the right. A roentgenogram of the chest revealed an old, probably quiescent, tuberculous infection in the upper lobe of both lungs. A ventriculogram visualized only the left lateral ventricle, which was displaced to the left. The third ventricle was also displaced to the left. This shift suggested a neoplasm in the right anterior temporal region.

Course.—A right temporal osteoplastic flap was turned on April 28, 1938. A large amount of meningiomatous tissue was removed from the floor of the right

middle fossa. The patient's condition was fairly good until toward the end of the operation, when the blood pressure dropped to 60 systolic and 40 diastolic. She recovered somewhat with stimulants and intravenous administration of fluids. Her condition remained fairly good until April 30, when the temperature rose to 106 F. rectally. The pulse became too rapid and weak to count. The respirations rose to 40 per minute. She died on the second postoperative day.

Autopsy Observations.—Instead of opening the skull in the usual manner, we first removed the occipital bone, then cut away the dura mater in this region and removed the cerebellum. We thus obtained a view of the inferior surface of the tentorial leaves and the dorsal surface of the brain stem as it passed through the incisura tentorii. This is illustrated in figure 3. The quadrigeminal bodies and the pineal gland were displaced to the left. The left superior and inferior quadrigeminal bodies were pressed against the free edge of the tentorium on the same side. Between the brain stem and the free edge of the tentorium cerebelli on the right several discolored protuberances were noted. These were indentified by further dissection as the herniated mesial portion of the right hippocampal gyrus.

The cerebral hemispheres were asymmetric. The right cerebral hemisphere was flattened in the region of the operative wound, which occupied the anterior two thirds of the lateral surface of the right temporal lobe. A good part of the superior and middle temporal gyri had been removed. The neoplasm indented the anterior end of the right temporal lobe rather deeply, was firmly attached to the sphenoid ridge anteriorly and was deeply embedded in the posterior part of the orbital portion of the right frontal lobe. It measured approximately 5 by 5 by 4 cm. and was easily separated from the underlying parenchyma. It displaced to the left the posterior ends of the gyri recti, the optic chiasm, the hypothalamus, the right uncus and the midbrain. There was a herniation of the right hippocampal gyrus so that the tentorial groove on its inferior surface was 1.3 cm. from the medial margin of the uncus. This compressed the tuber cinereum, the corpora mamillaria and the cerebral peduncles. There was also a tentorial groove on the inferior surface of the left uncus 4 mm. from the medial margin of that gyrus. The pineal and the splenium of the corpus callosum were shifted to the right (fig. 4).

Horizontal Section of the Cerebrum: The tumor invaginated the upper surface of the anterior end of the right temporal lobe and the adjacent opercular portion of the right frontal and parietal lobes and compressed the anterior end of the island of Reil. The anterior ends of the basal ganglia and the lateral ventricles were displaced to the left. The lumen of the right ventricle was reduced, while that of the left lateral ventricle was slightly dilated.

Microscopically, the neoplasm in the right sphenoid ridge proved to be a meningioma.

The midbrain was compressed from side to side. Many of the nerve cells in the nucleus of the third nerve and the adjacent nuclei showed swelling and an abnormal content of lipoid. Other nuclei and tracts were normal. There was a small mass of polymorphonuclear leukocytes and fibrin on the floor of the fourth ventricle. The medulla was entirely normal.

This case is clinically significant, for it was possible to suspect the occurrence of a hippocampal herniation preoperatively. The diagnosis was based on (1) the marked nuchal rigidity, (2) the changes in tonus

of the muscles of the extremities on passive movements of the head and neck (Magnus-de Kleyn tonic neck reflexes) and (3) pupillary irregularities, in association with signs and symptoms indicating a mass lesion of the right temporal lobe. It was also possible to prognosticate that any interference with the intracranial contents without correcting the compression of the midbrain by the herniated right hippocampal gyrus might result unfavorably.

Pathologically, one of the most important features of this case is the objective demonstration that hippocampal tissue is actually displaced medially into the space of Bichat and forced downward through the incisura tentorii into the posterior fossa. The shifted and compressed midbrain was observed and photographed in situ. This case assisted materially in confirming our previous assumptions as to the pathogenesis of the tentorial grooves. It also demonstrates the "strangulated" hippocampal herniation, a feature of this type of cerebral dislocation which we feel needs more attention because of its probable share in the fatal outcome. This case illustrates the fact that partial removal or decompression of the expanding intracranial lesion does not necessarily result in release of the herniated hippocampal gyrus. It would seem that any disturbance of equilibrium by any intracranial procedure, such as removing part or all of an intracranial mass, in the presence of a marked, strangulated hippocampal herniation is not necessarily the procedure of choice. Removal of the neoplasm may allow the brain tissue to shift back in the direction from which it had been shifted by the supratentorial mass, which, with the herniation staying in place, may further distort the mesencephalon and adjacent structures. This probably disturbs whatever equilibrium is already established and may precipitate a fatal chain of events.

CONCLUSIONS AND SUMMARY

Medial displacement and herniation of the hippocampal gyri into the space of Bichat and through the incisura tentorii occurred in 83 per cent of 100 cases of a supratentorial expanding lesion. Such herniations were present in most cases of increased intracranial pressure from any cause. Then they were rather narrow, slight and usually equal on the two sides. Midline and parasagittal lesions produced equal, marked herniations with little lateral difference. Unilateral cerebral lesions, in the temporoparietal region notably and in the temporal lobe particularly, produced a significant group of changes in the basilar region. These were: ipsilateral medial displacement and herniation of the hippocampal gyrus; contralateral shift of the brain stem, hypothalamus and optic chiasm and tracts with distortion of these structures, and, less frequently, hemorrhages in the brain stem and hippocampal, fusiform and occipital gyri. Of the important causative factors, the location and size of the

mass lesion were equally significant. The histologic type and rate of growth of the tumor mass were of questionable significance. Bilateral herniations tended to squeeze the brain stem and produce flattening of the mesencephalon with narrowing of the sylvian aqueduct.

A fairly consistent group of signs and symptoms were observed in conjunction with the temporal pressure cone. In order of frequency, they were: before operation (in the sense of any procedure which altered the intracranial pressure equilibrium), (1) fluctuations in state of consciousness, (2) anisocoria with or without disturbance in the light reflex, (3) nuchal rigidity, (4) imbalances of extraocular muscles, (5) cardiorespiratory and thermoregulatory disturbances, (6) paradoxic pyramidal tract signs and (7) "decerebrate rigidity"; and, after operation, (1) marked respiratory difficulties with failure of respiration before cessation of the heart action, (2) thermoregulatory disturbances and (3) cardiovascular difficulties. All signs and symptoms seem to have been exaggerated by lumbar puncture, encephalographic or ventriculographic examination or craniotomy. Supportive measures used to correct the dysfunctions enumerated were invariably futile.

It has been pointed out that the temporal pressure cone may produce false localizing, secondary or "distant" signs and symptoms in patients with expanding intracranial masses. We feel that the presence of this disastrous complication may be suspected clinically. We agree with Jefferson that it is essential to think of its possible occurrence in any case of tumor of the brain. It has been suggested that efforts to control the herniation might supersede other therapeutic procedures in certain cases.

Dr. Abner Wolf permitted us complete use of the pathologic material in this study.

INFLUENCE OF LOCOMOTION ON THE PLANTAR REFLEX IN NORMAL AND IN PHYSICALLY AND MENTALLY INFERIOR PERSONS

THEORETIC AND PRACTICAL IMPLICATIONS

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The extensor response of the big toe, or the Babinski sign, can in certain persons be induced by physical exertion. This fact is not generally known, even among neurologists. The purpose of this study is to show that the occurrence of a Babinski sign following exertion has a characteristic relation to the type of exertion and to such factors as a history of prenatal and early postnatal developmental abnormalities, influencing the ultimate constitutional organization of the individual. Herein lie, we believe, the important theoretic and practical implications of the "exertion Babinski."

OBSERVATIONS

Effect of Exertion on the Plantar Reflex in a Group of One Hundred and Sixty-Eight Normal Persons.—The plantar reflex was tested in a group of 168 college students in a Reserve Officers Training Camp before and after a maneuvering exercise. A normal plantar flexor response of the big toe was present in all but 1 of 168 men. In 1 a unilateral Babinski sign was elicited. At 3 p. m. these 168 men departed with light packs and regulation rifles on a march through open country and returned to the base camp at 6 a. m., having covered a total distance of about 14 miles (22.4 kilometers). No change occurred in the behavior of the plantar reflex in 156 of 168 young men, including 1 with a unilateral extensor response, whereas a Babinski sign developed in 12, or 7.2 per cent. In 10 of these, or 6 per cent of the total number, a Babinski sign developed unilaterally and in 2, or 1.2 per cent, bilaterally.

The men in the group had passed a physical examination for military service which would exclude any conspicuous medical, psychiatric or neurologic abnormalities. Their ages varied between 18 and 28 years, and their intellectual level must be assumed to be equal to or above the average. The conditions under which the exertion was endured by them were uniform, for the march was a strictly regulated military drill.

Effect of Ordinary Work on the Plantar Reflex in a Group of Two Hundred and Twenty-Nine Mentally Defective Adults in a Farm Colony.—Having obtained a relative measure of the effect of exertion in the form of a march on the plantar reflex in a group of normal persons, we then made a study of the effect of ordinary work on the plantar reflex in a selected group of 229 physically inferior and mentally defective men at a farm colony connected with the Walter E. Fernald State School.

The psychometric intelligence level of the group in terms of the intelligence quotient was 0.44, the lowest being 0.19 and the highest 0.73. Two thirds of the group were represented by "imbeciles" with an intelligence quotient below 0.50, and one third were in the category of "morons," with an intelligence quotient above 0.50. The average age of the group was 33 years, the youngest being 17 and the oldest 68. Three fourths of the group were less and one fourth were more than 40 years of age. Their average height was 5 feet 5 inches (165 cm.) and their average weight 127 pounds (57.6 Kg.). Few could be regarded as fair physical specimens; that is, by physical, as well as by intellectual, standards they were inferior to a group of healthy young adults eligible for military service.

The plantar reflex was examined at 5 a. m., while all the men were in bed. In 218 of the 229 subjects the plantar reflex was a normal flexor response of the big toe bilaterally, and in 11 either a frank unilateral extensor response (6 subjects) or a unilateral tendency to an extensor response (5 subjects) was elicited. At 8 a. m. the men went to work, which consisted in sawing and stacking wood in the wood yard. At 5 p. m., that is, after seven hours of routine work, 180 of the 229 subjects showed no change in the behavior of the plantar reflex from that recorded at 5 a. m., whereas in 49, or 21.4 per cent, a definite change occurred in the behavior of the plantar reflex, as follows: A tendency to an extensor response appeared in 12, or 5.2 per cent of the total number; a frank unilateral extensor response developed in 24, or 10.5 per cent, and a bilateral extensor response developed in 13, or 5.7 per cent.

Control Examination of the Plantar Reflex at Different Hours of the Day.—Thirty-eight of the 49 "positive" subjects, in whom an extensor response developed after a day's work, and 14 of the 180 "negative" subjects, who showed no such change in the plantar reflex, were examined again a few days later at 5 a. m., at 9 a. m., at 3 p. m., at 5 p. m. and at 7 p. m., that is, after two hours' rest. The results of these control examinations may be summarized as follows: The behavior of the plantar reflex under the same type of exertion may vary in some persons from day to day. This occurred in 2 previously "positive" subjects who became "negative" and in 2 previously "negative" subjects

who became "positive" when reexamined on another day. However, in an absolute majority, namely, in 95 per cent of the "positive" and in 86 per cent of the "negative" subjects, the behavior of the plantar reflex remained remarkably constant. A change in the plantar reflex may manifest itself within a few hours after the commencement of exertion. This was shown by 5 subjects who at 5 a. m. had a normal flexor response and at 9 a. m. showed already a tendency to an extensor response. As the exertion continued the extensor response tended to become more conspicuous and to occur more frequently and by 3 p. m. nearly two thirds (61 per cent) of the "positive" subjects exhibited either a tendency to or a frank extensor response. If a unilateral extensor response developed on one day, it consistently occurred on the same side on another day. Once an extensor response developed during the day, it still persisted at 7 p. m. in 27 per cent of the subjects; however, in 73 per cent of the subjects a rest of two hours restored a normal flexor response.

Effect of Progressive Locomotion.—Work in the wood yard implied, of course, upright locomotor activity. However, a sustained march, unlike the exertion of being up and moving about while sawing and stacking cordwood, is a type of exertion which consists of a highly stereotyped and uniform neuromuscular activity. In order to ascertain the effect of progressive locomotion on the plantar reflex, 60 subjects were selected from the group of 180 who remained "negative" after the work in the wood yard. The average age of the group was 22 years, i. e., 11 years younger than the average age of the entire group. The plantar reflex was examined again at 7 a. m. At 8 a. m. the group departed on the first stage of a march 10 miles (16 kilometers) long. This distance was covered in two and a half hours. At the termination of this stage of the march it was found that in 8 men a Babinski sign developed, either unilaterally (7) or bilaterally (1).

After three hours' rest the group departed on the second stage of the march, covering a distance of 14 miles (22.4 kilometers) in three and a half hours. After the completion of the march it was found that the subjects in whom an extensor response developed at the end of the first stage of the march showed no further change in the behavior of the plantar reflex, while 6 new subjects who still had a flexor response after the first stage of the march now showed a Babinski sign, 4 unilaterally and 2 bilaterally.

Thus, of a group of 60 young physically inferior and mentally defective adults who previously had endured a seven hour day of routine farm work without the development of a Babinski sign, 13.3 per cent after a march of 10 miles and a total of 23.3 per cent after an additional

march of 14 miles exhibited a Babinski sign, either unilaterally (11 subjects) or bilaterally (3 subjects).

Sign of Fanning Toes.—The fan sign occurred in 13 of 229 subjects examined. In 2 a fan sign and an extensor response of the big toe developed on the same side. However, in most of the subjects the occurrence of a fan sign and the pattern of response of the big toe were independent. Thus, in 7 subjects a fan sign developed without a change in the flexor response of the big toe on either side, and in 3 subjects an extensor response of the big toe developed on the opposite side. It is noteworthy that at 5 a. m., that is, before exertion, the fan sign was present in only 2 of the 229 subjects examined, or in less than 1 per cent; it developed after a day's work in 6 subjects, or in 2.6 per cent. After a march of 10 miles a fan sign developed in only 1 of the group of 60 subjects, or in less than 2 per cent, but after a second stage of march (14 miles) it developed in 6, or 10 per cent, of the subjects.

Other Effects of Exertion.—Among the other effects of exertion the following changes were noteworthy: The threshold of the plantar reflex became higher after exertion. The extraordinary sluggishness and hesitancy of the response when examined after exertion contrasted with the facility with which a specific reaction of the toes was elicited in the morning before arising. Circulatory disturbances of the extremities, consisting of a purplish mottled cyanosis, sweating and a perceivable fall in cutaneous temperature of the feet and toes, were conspicuous after exertion. The outstanding feature was an extraordinary increase in paratonic rigidity. This was a changing type of rigidity which, objectively, consisted of involuntary anticipation of and compulsive resistance to all passive movements and utter inability voluntarily to relax an extremity or part under examination, in spite of manifest good will on the part of the subject to do so. Many of the subjects examined were aware of their "stiffness," and the more conscious they were of it the greater was the anticipatory and compulsive fixation of the extremity under examination.

Comment.—In summing up the foregoing observations, one may state that the occurrence under exertion of a Babinski sign is a consistent, and not an accidental, phenomenon. Locomotion in the form of a march appears to be particularly effective in bringing about an extensor response. In the group of constitutionally inferior persons represented by mental defectives in a farm colony the Babinski sign developed distinctly more readily than in the representative group of normal subjects in a military training camp. A rest of a few hours after exertion restored a normal flexor response. The fan sign was largely independent of the type of response of the big toe and occurred less frequently. It developed when a more severe degree of exertion

was reached. Among other effects of exertion, rise of threshold of the plantar reflex, circulatory disturbances and increase in paratonic rigidity were particularly conspicuous.

FACTORS INFLUENCING PLANTAR RESPONSE UNDER EXERTION

A number of factors may influence the behavior of the plantar reflex under exertion.

Neurologic Status.—Neurologic examination revealed more or less conspicuous preexisting abnormalities in 34 per cent of the "positive" and in 12 per cent of the "negative" subjects. In the group of "positive" subjects a Babinski sign developed consistently on the side of the preexisting additional signs of pyramidal deficiency, such as exaggeration of tendon reflexes, Barré's sign, combined flexion of the leg on the thigh and foot clonus. In subjects in whom a bilateral Babinski sign occurred after exertion, the extensor response developed first on the side of the preexisting additional signs and, after cessation of exertion, persisted longer on that side. It is of some interest, however, that of the 6 subjects in whom a unilateral extensor response with other signs of pyramidal deficiency existed before the commencement of exertion, in only 1 did an extensor response develop on the other side and in 5 no change occurred in the behavior of the plantar reflex. These observations show that a focal or diffuse lesion of the nervous system is a definite factor in causing an "exertion Babinski" to develop. However, the presence of a focal lesion involving the corticospinal system on one side only does not necessarily render the contralateral corticospinal system less resistant to the effects of exertion.

Fatigue.—The results of examination of the plantar reflex during and after exertion showed that with the increase in duration and severity of exertion the extensor response developed more frequently and became more conspicuous and the threshold of response rose concurrently. On the other hand, a rest of one to two hours restored a normal flexor response in most of the subjects. It should be evident that fatigue was a specific factor in causing the changes in the plantar reflex to develop.

Age.—The group of mentally defective subjects were from 8 to 10 years older than the group of students in the military training camp, and in the former group 49 "positive" subjects were on the average 4 years 7 months older than 180 "negative" subjects, the average ages being 35 years 4 months and 30 years 9 months, respectively. However, it is of interest that in the group of "positive" subjects, 13 who showed a bilateral extensor response after exertion were the youngest (average age 31 years 3 months), 24 in whom a unilateral extensor response developed were 3 years older (average age 34 years 5 months) and 12 in whom only a tendency to an extensor response appeared (in 11

unilaterally) were the oldest (average age 36 years 8 months). This correlation shows that the role of age is relative and that other factors must play a part. These will presently be made evident.

Other Factors.—Premature birth, birth injuries, infantile convulsions and acute diseases of the nervous system in infancy or early childhood were characteristically more frequent in the history of the mentally defective subjects in whom a Babinski sign developed than in those in whom no change occurred in the plantar reflex. Information concerning the history of early infancy and childhood was available for 109 subjects in whom the Babinski sign did not develop under exertion and for 34 in whom it appeared. Singly or in combination, premature birth, birth injury, diseases of infancy and early childhood with cerebral complications and infantile convulsions were recorded for 44 per cent of the subjects in whom the plantar response did not appear with exertion and for 68 per cent of those in whom it did develop. It is noteworthy that "acquired" factors, such as birth injuries and diseases of childhood, were recorded with nearly equal frequency for the "positive" (26.8 per cent) and for the "negative" (23.2 per cent) subjects. On the contrary, the prenatal and inborn factors, such as prematurity of birth and convulsive diathesis in infancy and childhood, were recorded twice as often in cases of the "positive" (41.1 per cent) as in those of the "negative" (21.2 per cent) subjects. Thus, it should be evident that in the appearance of a Babinski sign under exertion, the role of congenital (constitutional) factors is distinctly greater than that of acquired factors operating on the child at or after birth.

This argument is further supported by a characteristic correlation between the occurrence of a Babinski sign under exertion and the age of establishment of upright locomotion and of articulate speech.

It is generally accepted that an average normal child walks and talks at 1½ years of age. The group of "negative" subjects walked on the average one year later and talked one and a half years later than normal persons. The group of "positive" subjects was distinctly more delayed in the development of locomotion and speech, for the persons of this group walked on the average one and a half years later and talked two and a half years later than the average normal subject. The significance of this correlation became enhanced when it was found that in the group of "positive" subjects 6 in whom a tendency to an extensor response developed without a frank Babinski sign walked on the average at the normal age of 1½ years and talked at 2½ years; 19 in whom a frank Babinski sign developed on one side only were more retarded in locomotion and speech, for they walked on the average at 3 years and talked at 3½ years, and 9 subjects in whom a Babinski sign developed

bilaterally were the most retarded in locomotion and speech, for they walked on the average at 3½ years and talked at 4½ years.

These correlations show that the occurrence of a Babinski sign after exertion is largely conditioned by the history of early development of the subject's cerebral functions and that in the final count the factors which determine the ultimate constitutional organization of the person are most decisive.

In the group of mentally defective persons the average intelligence quotients of the "negative" and of the "positive" subjects were identical, being 0.44 for each group. Also, in regard to general physical habitus in terms of average heights and weights, no difference was appreciable between the "positive" and the "negative" group. Thus, within a relatively homogeneous group of physically and mentally inferior subjects the psychometric intelligence level and the general "physique" showed no relationship whatever to the behavior of the plantar reflex, although within the range of as wide a difference as that between a group of mentally defective persons and a group of college students eligible for military service a higher intelligence level and a superior "physique" appear to be concordant with the lesser incidence of a Babinski sign under exertion. It should be evident, therefore, that it is not the "intelligence" or the "physique" that influence the behavior of the plantar reflex under exertion but the factors of which the mental and physical inferiority is the effect.

THEORETIC CONSIDERATIONS

The plantar reflex in man is differentiated into two patterns—the extensor and the flexor response of the big toe. This differentiation is a specifically human attribute.[1] At birth the isolated dorsal extension of the big toe, associated with spreading or fanning of the other toes, differentiates from what may be termed the fetal, prevalently flexor pattern of the plantar response and coincides with the myelination of the suprasegmental tracts, which connect the cord with the postural mechanisms of the tegmentum of the brain stem.[2] The infantile extensor response may therefore be looked on as the first step in the upbuilding of erect posture. It is, as a rule, associated with contraction of the extensor muscles of the leg and is influenced by body posture. It is noteworthy that the extensor response is always most readily elicitable from the

1. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

2. Minkowski, M.: L'état actuel de l'étude des réflexes, Paris, Masson & Cie, 1927. Tournay, A.: Le signe de Babinski. Rapport de neurologie, Trentième Congres des médecins aliénistes et neurologists de France, Génève-Lausanne, 1926, Paris, Masson & Cie, 1926.

outer border of the sole, which is a specific reflexogenic zone for this pattern of response.

Coincidentally with the myelination of the cortical projection systems and the establishment of erect locomotion, that is, between 9 and 18 months of age, the flexor response associated with a contraction of the flexor muscles of the leg becomes the only pattern of the plantar reflex accessible to stimulation from any part of the sole. However, it is first and more readily elicitable from the inner border of the sole, especially by stimuli endowed with nocuous qualities, i. e., stimuli potentially injurious to the skin. The relative specificity of the receptive fields of the extensor and the flexor pattern of the plantar reflex and the "local sign" of each pattern of response furnish evidence of their "purposive" character. The extensor response of the big toe flattens the arch of the foot and, associated with the contraction of extensor muscles of the leg, aids in locomotion in supporting the gravity of the body on the narrow base of one foot while the other foot is withdrawn from the ground. The flexor response increases the arch of the foot and, contrary to the views advanced by Walsh and contested by Babinski,[3] represents a part of the reflex flexion withdrawal when, in locomotion, the sole of the foot comes in contact with injurious stimuli of the ground. Thus, whereas the extensor pattern of the plantar response is essentially a "postural" (proprioceptive) component of the plantar reflex, the flexor pattern appears to be an essentially "phasic" (exteroceptive and nociceptive) component.

Such an interpretation of the plantar reflex conforms to the evidence that the flexor response of the big toe in man and primates depends specifically on the functional differentiation of the "motor" cortex—area 4 of Brodmann.[1] Ablation of area 4 causes flaccid paralysis of the contralateral extremities and leads to loss of the cortical, "phasic" differential of the plantar reflex and emergence of the subcortical, "postural" differential of the reflex in the form of a Babinski sign. In this connection the specific effect of locomotion becomes of distinct theoretic interest. Indeed, area 4 in man differentiates from what essentially is a "locomotor" cortex of lower mammals. Sustained locomotion, such as a march, which consists of uniform and stereotyped movements, leads to loss of the cortical flexor differential and release of the extensor differential of the plantar reflex more readily than other forms of motor activity, such as work in the wood yard, because the locomotion requires a uniform and more locally restricted cortical activity and so leads more readily to a state of fatigue in area 4. However, the occurrence after prolonged locomotion of a fan sign shows that the cortical deficit induced

3. Babinski, J.: Réflexes de défense: Address before the Royal Society of Medicine, London, March 31, 1922, Brain **41**:149, 1922; in Barré, J. A., and others: Oeuvre scientifique de J. Babinski, Paris, Masson & Cie, 1934.

by exertion tends eventually to become more generalized and spreads beyond area 4, involving the anteriorly situated premotor area 6 as well.[4] The increase after exertion of autonomic disturbances, such as cyanosis, sweating and lowering of temperature of the extremities, also points to functional upsets in the premotor cortex.[5] This contention is further supported by the characteristic increase, after exertion, of paratonic rigidity. In the light of recent experimental evidence, we are inclined to assimilate the paratonic rigidity and associated motor disturbances with the changing spasticity, forced grasping, resistance to passive manipulation and "retardation of motor adjustments" described by Fulton and his co-workers in monkeys after bilateral ablation of the premotor cortex.[6]

The observations presented invite the inference that a Babinski sign, fan sign, autonomic disturbances and paratonic rigidity occurring after relatively moderate exertion reveal a weakness of the cortical "dominance" in the nervous integration of a constitutionally inferior person.

PRACTICAL IMPLICATIONS

It has been shown that fatigue in the sense of diminution of excitability of the motor cortex is a specific factor in bringing about an extensor response under exertion. It is reasonable to assume that under sufficiently severe exertion potentially even a healthy and vigorous person may literally "turn up his toes." However, such an effect of exertion depends, other conditions being equal, largely on the history of the early development of the cortical mechanism of upright locomotion, for a gross delay in the differentiation of locomotor functions during infancy and childhood is significantly and consistently reflected in the occurrence of a Babinski sign under relatively moderate exertion. In this sense the behavior of the plantar reflex under exertion may be looked on as a pertinent indicator of the constitutional stamina of the subject. It is in the field of military medicine that the observation presented should be especially useful. A recruit who after a march of a few miles or at the end of a day of routine work shows a bilateral extensor response, regardless of his intellectual and physical status otherwise, is a poor choice for assignment to an active infantry unit or a scouting detachment, although he may be proficient in other military services.

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4. Kennard, M. A.: The Localizing Significance of Spasticity, Reflex Grasping, and the Signs of Babinski and Rossolimo, Brain **56**:213, 1933.

5. Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, Arch. Neurol. & Psychiat. **33**:537 (March) 1935.

6. Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, Arch. Neurol. & Psychiat. **31**:221 (Feb.) 1934.

PATTERNS OF CEREBRAL INTEGRATION INDICATED BY THE SCOTOMAS OF MIGRAINE

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The scotomas characteristic of ophthalmic migraine have been described by a number of investigators.[1] The visual disturbance precedes or accompanies other symptoms of migraine and is usually of short duration. It is generally restricted to one half of the visual field, the right or the left, and ranges in size from a scarcely noticeable blind-spot to total hemianopia. A great variety of forms have been mentioned in the literature, but those which have been described in detail are of much the same type. The scotoma starts as a disturbance of vision limited to the neighborhood of the macula and spreads rapidly toward the temporal field. With increase in size the disturbed area moves or "drifts" across the visual field, so that its central margin withdraws from the macular region as its peripheral margin invades the temporal. Spread from the temporal toward the macular region has also been described and is apparently more frequent when complete hemianopia develops. The area may be totally blind (negative scotoma), amblyopic or outlined by scintillations. A scotoma of the last type takes the form of "fortification figures," so called from the suggestion of a map of the bastions of a fortified town. They appear as series of parallel, white or colored scintillating lines, forming angles or polygons along the margins of the scotomatous area. The scotomas are symmetric for the two eyes and so are almost certainly the result of a cortical disturbance.

Two characteristics of the scotomas have not previously been reported and are of some interest as suggesting the nature of the inherent organization of cortical activity. These are (1) the maintenance of the characteristic shape of the scotoma during its drift across the visual field and (2) the "completion of figure" described by Gelb and by Poppelreuter as occurring in scotomas of traumatic origin.

Over a period of years I have had opportunity to observe and map a large number of such scotomas, uncomplicated by any other symptoms

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From Harvard University.

1. For an account of the symptomatology of ophthalmic migraine, with references, see H. Richter (in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 17, pp. 166-345). The most detailed description of scotomas is that of F. Jolly (Ueber Flimmerskotom und Migräne, Berl. klin. Wchnschr. **39**:973-976, 1902).

of migraine. The scotoma usually occurs first as a small blind or scintillating spot, subtending less than 1 degree, in or immediately adjacent to the foveal field. This spot rapidly increases in size and drifts away from the fovea toward the temporal field of one side. Usually both quadrants of one side only are involved, the right and the left being affected with about equal frequency. Occasionally the scotoma is confined to one quadrant. Rarely, there is complete hemianopia, and in 1 instance, in more than 100, there was complete blindness in both lower quandrants, with sparing of the macula.

RATE OF DRIFT

The outline of the scotoma is readily charted by fixating a mark on a sheet of paper, moving a pencil toward the blind area along dif-

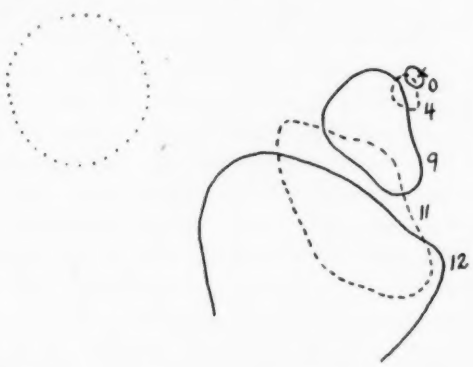

Fig. 1.—Maps of a negative scotoma confined to the lower left quadrant. The successive sketches were made at intervals of no, four, nine, eleven and twelve minutes after the area was first noted. Alternate sketches are outlined with broken lines to avoid confusion. The fixation point is marked by ×. The dotted circle is an outline of the blindspot of the homolateral eye, to indicate the size of the visual field. In this instance the form was not well maintained.

ferent radiuses and marking the places at which the point of the pencil disappears—the usual method for crude demonstration of the blindspot. When this is done, each scotomatous area is found to have a distinct shape, and when the charting is repeated at brief intervals, this specific shape is roughly preserved as the area drifts across the visual field. Figures 1, 2, 3 and 4 show the successive positions and shapes of four such areas charted at intervals of from two to five minutes. Occasionally the shape is not well preserved, as in the area shown in figure 1. Generally, however, within the region between the macula and

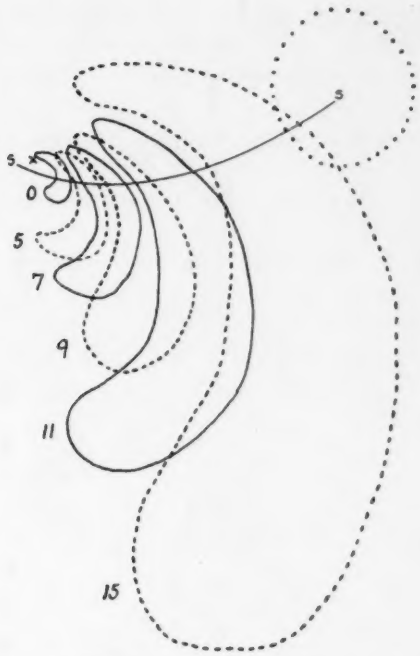

Fig. 2.—Maps of a scintillating scotoma sketched at the intervals, expressed in minutes, shown at the left. Scintillations were confined to the region above the line *s-s*. Arrangement as in figure 1.

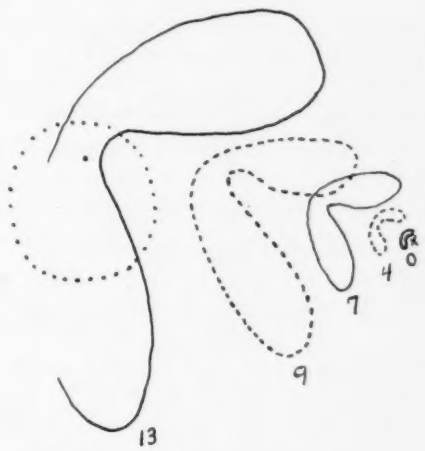

Fig. 3.—Successive maps of a negative scotoma, arranged as figure 1.

the optic disk [2] the form is maintained, as shown in figures 2 and 4, and occasionally, as in figure 3, successive charting reveals almost perfect correspondence of forms. As the scotoma drifts to the temporal field accurate mapping becomes impossible, since the pencil point can no longer be clearly seen.

Not only does the form of the scotomatous area remain constant as it drifts across the visual field, but when there are fortification figures, these also maintain their characteristic pattern in each part of the area. The size of the fortification figures does not increase with increase in the size of the scotoma, but additional figures are added as the area grows. It is not possible to sketch the figures accurately. The rate of scintillation is near 10 per second [3] and the form changes rapidly, but small figures can be distinguished from large and simple angles from polygonal figures. Differences of the sort indicated in figure 5 are unmistakably

Fig. 4.—Successive maps of a scintillating scotoma to show characteristic distribution of the fortification figures. The × in each case indicates the fixation point.

present and persist while the area drifts for considerable distances across the field. I have the impression, without adequate data to confirm it, that the size and shape of the fortification figures are constant for each radius of the field. That is, the pattern is finer and less complicated in the upper quadrants than in the lower, as indicated in figures 4 and 5. If true, this suggests that the pattern is a function of the anatomic substratum, rather than of the nature of the propagated disturbance.

2. The blindspots do not, of course, interfere with binocular charting of the scotoma. In the figures the outline of the blindspot of the homolateral eye is inserted to indicate the position and size of the scotoma in relation to the visual field.

3. This rate is above the maximum for counting but well below the flicker fusion point. The rate may be related to the alpha rhythm.

More certainly, when the fortification figures are limited to one part of the area, they continue in that part only throughout the entire drift, as shown in figure 2.

Whatever the precipitaing cause of the disturbance, these facts indicate that an inhibitory process, in the case of blind areas, or an excitatory process, in the case of scintillations, is initiated in one part of the visual cortex and spreads over an additional area. As the process spreads, activity at the point where it was initiated is extinguished, and the process of extinction also spreads over the same area at about the same rate as does the active process.

The increase in size of the scotoma as it passes toward the peripheral areas does not necessarily mean that the disturbance starts from a point and spreads to larger areas. Apparent size in the visual field is not

Fig. 5.—Sketch to show apparent differences in fortification figures. The coarser and more complicated figures are generally in the lower part of the field.

related to the size of the excited region of the striate cortex, since the cortical field of the macula is probably as large as that of all the remaining retina.[4] Apparent size must be determined at a later stage of integration, and in the case of smaller scotomas the actual extent of cortical area involved in the disturbance is probably constant as the disturbance drifts.

The drift of the scotomatous area is what might be expected from the spread of excitation across a succession of reverberatory circuits, as described by Lorente de Nó,[5] with the activity of the circuits extinguished at the inner margin of the blind area at the same rate as it is

4. Poliak, S.: The Main Afferent Fiber System of the Cerebral Cortex in Primates, Univ. California Publ. Anat. **2**:1, 1932.

5. Lorente de Nó, R.: Analysis of the Activity of the Chains of Internuncial Neurons, J. Neurophysiol. **1**:207-244, 1938.

propagated to new circuits at the advancing margin. The rate of propagation may eventually have some significance. For a number of observations the rate is fairly uniform. Ten to twelve minutes is required for spread of the outer margin from the region of the macula to the blindspot of the homolateral eye. The rate beyond this point is rapid and difficult to estimate, but the total time required for the disturbance to spread from the macular area to the temporal field is approximately twenty minutes. A negative area of the size shown in figure 2 is determined by an inhibitory phase lasting for about five minutes. The development and the recovery of complete hemianopia each requires about fifteen to twenty minutes, indicating a propagation of the disturbance at about the same rate, with a longer period of inhibition, sometimes lasting half an hour.

The anteroposterior length of the striate area is about 67 mm.[6] The disturbance starts very near the midline of the visual field, which is probably projected near the occipital pole; propagation to the temporal margin requires about twenty minutes. These figures give a rate of 3 mm. per minute or less for the propagation of the disturbance.

In each attack the disturbance seems to spread with different characteristics along different radiuses of the visual field. Thus, in the scotoma sketched in figure 2 scintillations were confined to the upper quadrant and the duration of the inhibited phase was apparently greater in the lower part of the field than in the upper, as measured by the width of the band. The constriction in the band, shown in figure 3, indicates a negative phase of short duration, passing out along a definite radius above the margin of the lower quadrant. Poppelreuter[7] has pointed out that in scotomas of traumatic origin there are indications of dynamic organization of the visual field such that effects of fatigue, etc., tend to spread along the radiuses of the field, and the evidence from the scotomas of migraine leads to a similar conclusion. No anatomic basis for such phenomena is known at present, but some anteroposterior polarization of the striate cortex is indicated.

The scintillations must represent a phase of intense excitation. The lines are of dazzling brightness, subjectively of the order of direct sunlight reflected from a white surface. They occur along the advancing margin of the area,[8] followed by the blind region, as if a wave of strong excitation were followed by a phase of total inhibition (fig. 4). However,

6. Filimonoff, I. N.: Ueber die Variabilität der Grosshirnrindenstruktur, J. f. Psychol. u. Neurol. **44**:1-96, 1932.

7. Poppelreuter, W.: Die psychischen Schädigungen durch Kopfschuss im Kriege 1914-1917, Leipzig, L. Voss, 1917.

8. In the early stages, when the area is near the macula, it may be entirely filled with scintillations, but later these form a band of varying width along the advancing margins. Circular bands radiating from a point have been reported.

part or all of the area may show no signs of excitation, yet advance at the same rate (fig. 2, lower part). From this it seems that the inhibitory phase may spread without a preliminary phase of excitation, and at the same rate. Occasionally the negative phase fails to develop, and objects may be seen in the field immediately behind, or even between, the fortification figures, as shown in the sketches of Jolly.[1] The propagation of the excitatory phase with or without a subsequent protracted inhibitory phase and the propagation of the inhibitory phase without evidence of previous excitation raise an important problem of the interrelations of these processes.

LIMITATION OF SPREAD

The definite limitation of symptoms to those of primary visual disturbance argues for a sharp functional separation of the striate areas from adjacent regions of the cortex. The disturbance, spreading as a scintillating or negative scotoma, is evidently intense, or at least dominant over other cortical activities; yet it appears to be blotted out completely at the margin of the striate cortex. Except for a very slight torticollis associated with complete hemianopia, I have been unable to detect any additional symptoms during or after the scotoma. It seems to move off the side of the visual field and leave no after-effects whatever. The absence of any symptoms associated with the peristriate areas indicates that the disturbance does not spread beyond the margin of the primary visual cortex. The interconnections between architectonic areas must therefore be of a very different nature from those of a single area.

In experiments with animals I have been unable to demonstrate any symptoms of visual disturbance after knife cuts which partially sever the striate cortex from surrounding areas, even when difficult problems of visual generalization are used in the tests.[9] The complete blocking of the excitatory wave of the scotoma suggests that in man also there may be a greater autonomy of function in the different architectonic areas than is generally assumed to be the case.

REPETITIVE PATTERNS

The activity within the scintillating area is perhaps of some theoretic interest. The scintillations have the form of distinct parallel lines, which cannot be counted but give the impression of groups of five or more. These seem to sweep across the figure toward the advancing margin and are constantly renewed at the inner margin, like the illusion of movement of a revolving screw. The pattern of lines and angles is much the same in the experience of all persons who have reported them. Its significance is in the reduplication of activity throughout a considerable

9. Lashley, K. S.: The Mechanism of Vision: XVII. Autonomy of the Visual Cortex, J. Genet. Psychol., to be published.

area. Repetitive patterns of activity have been reported in other cases of pathologic cortical activity. They are frequently mentioned as characteristic of the visual hallucinations following mescal poisoning,[10] and perhaps are represented on the motor side by the convulsive movements of an epileptic attack.

Such repetitive patterns should be predicted from the free spread of excitation through a uniform neural field having the structural arrangement of reverberatory circuits described by Lorente de Nó.[11] Although nothing is known of the actual nervous activity during the migraine, the picture suggests that the propagated disturbance is so intense as to be independent of the afferent supply of the cortex and that the patterning represents the type of organization into which the cortical activity falls as a result of inherent properties of the architectonic structure. I have elsewhere outlined briefly a theory of cortical integration based on interference of spreading waves of excitation,[12] and the patterning shown in the migraine scotomas is consistent with that theory.

COMPLETION OF FIGURE

The "principle of completion" in visual organization was first pointed out by Fuchs [13] and confirmed by Poppelreuter.[7] It states that certain simple geometric patterns (square, circle, triangle, stripes) when exposed so that a part falls within the blind field of a patient with hemianopia of traumatic origin are always perceived as complete figures, although it is certain that the part falling within the scotomatous area is not actually seen. When the migraine scotoma is without scintillations the same phenomenon may be observed. Two examples stand out in my experience in which there was opportunity for careful observation.

A negative scotoma may completely escape observation, even when it is just off the macula, unless it obscures some object to which attention is directed. Talking with a friend, I glanced just to the right of his face, whereon his head disappeared. His shoulders and necktie were still visible, but the vertical stripes in the wallpaper behind him seemed to extend right down to the necktie. Quick mapping revealed an area of

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10. Klüver, H.: Mescal, London, Kegan Paul, Trench, Trubner & Company, 1928, pp. 1-111.

11. Lorente de Nó, R.: Studies on the Structure of the Cerebral Cortex: II. Continuation of the Study of the Ammonic System, J. f. Psychol. u. Neurol. **46**:113-177, 1934.

12. Lashley, K. S.: Mass Action in Cerebral Function, Science **73**:245-254, 1931.

13. Fuchs, W.: Untersuchungen über das Sehen der Hemianopiker und Hemiamblyopiker: II. Die totalisierende Gestaltauffassung, in Gelb, A., and Goldstein, K.: Psychologische Analysen hirnpathologischer Fälle, Leipzig, J. A. Barth, 1920, pp. 419-561.

total blindness covering about 30 degrees, just off the macula. It was quite impossible to see this as a blank area when projected on the striped wall or other uniformly patterned surface, although any intervening object failed to be seen.

On another occasion, with complete hemianopia, including the macula, it was possible to divide a complex object on any line of fixation. A human face was sharply divided by fixating the tip of the nose, so that half, including one nostril only, was visible. At the same time it was impossible so to fixate a circular object that only half was seen. Fixating a chalk mark on the middle of a billiard ball failed to make any part of the ball invisible, although the ball was considerably larger than the readily divided nose.

These observations are of interest as showing that filling in the blindspot and the completion of figures in scotomatous areas are not the result of habits of disregarding blind areas or of identifying part figures. The phenomena appear immediately with new blind areas. They must, then, represent some intrinsic organizing function of the cortex. The figures completed are reduplicated patterns or very simple symmetric figures. The relation of this fact to the tendency to reduplication in fortification figures and other patterns of "spontaneous" activity of the visual areas is suggestive of a common mechanism.

Such phenomena can be made intelligible by the assumption that the integrative mechanism of the striate cortex tends to reproduce a pattern of excitation, aroused in one region, in any other region also if the latter is not dominated by different afferent patterns. Such a reduplication of patterns should result from the spreading of waves of excitation from points of initial stimulation, by analogy with the transmission of wave patterns on the surface of a liquid. Recent work on the histology of the cortex reveals an anatomic basis for radiation of such waves, in that the interconnections are so numerous as to constitute virtually a homogeneous conducting mechanism.

SUMMARY

Maps of the scotomas of ophthalmic migraine sketched at brief intervals during an attack suggest that a wave of intense excitation is propagated at a rate of about 3 mm. per minute across the visual cortex. This wave is followed by complete inhibition of activity, with recovery progressing at the same rate. Sometimes the inhibition spreads without the preceding excitatory wave. Limitation of the disturbance to the primary visual cortex raises questions as to the nature of the interconnections between architectonic fields. The observations are interpreted in relation to the possible integrative effects of radiating waves of excitation in the cortex.

Case Reports

ANOSOGNOSIA AND AUTOTOPAGNOSIA

CLARENCE W. OLSEN, M.D., AND CARL RUBY, M.D., LOS ANGELES

The syndrome of unawareness of hemiplegia described by Babinski under the name anosognosia has been shown by Barkman [1] to occur in connection with a lesion of the right thalamus. Von Hagen and Ives [2] recently reported 2 cases in which the syndrome was present and in which autopsy demonstrated a lesion not in the thalamus but so situated as to cut off the connections between the thalamus and the entire cerebral cortex except, perhaps, the occipital pole. In either case it would seem that the lesion was capable of producing both hemiplegia and hemianesthesia. In the case to be reported here the patient, who had hemiplegia with crural dominance from softening of the paracentral lobule, failed to recognize her paralysis owing to a lesion affecting the temporoparietal cortex on the same side.

REPORT OF A CASE

Schoolteacher, woman, aged 67, with diabetes mellitus, arterial hypertension and recent difficulty in remembering proper names. Paralysis of right leg and weakness of right arm. Agraphia, acalculia, finger agnosia, confusion of right and left and variable alexia and constructive apraxia. Anosognosia for paralysis of right extremities. Right hemianopia, acoustic verbal agnosia, amnesic aphasia and perseveration. No color agnosia nor visual agnosia for objects. Sudden death. Autopsy: Coronary arteriosclerosis. Recent softening of left paracentral and upper precentral and postcentral gyri and also of left angular gyrus and underlying white centrum. Old vascular lesion of left caudate nucleus.

Mrs. L. P., a widowed octoroon aged 61, was admitted to the White Memorial Hospital under the care of Dr. C. B. Coggin on March 29, 1939, because she had suffered from loss of function of her right arm and leg for a week and incontinence of urine for three days.

The patient had had uncontrolled diabetes mellitus for eleven years and high blood pressure for an indefinite period. Her relatives had noticed for some time that she had difficulty in recalling their names. Ten days before admission she complained of headaches and dizziness, which were severe enough to make her take to bed. These symptoms were accompanied by increasing weakness of the right leg so that she had to be helped to go to the bathroom. The family also reported diminished sensation in the arm and leg on the right side, but the patient complained that the right arm was sore when touched. Three days before admission she began to have fecal and urinary incontinence, and the day before admission she said things looked blurred. The family believed that her memory had been failing, since she did not answer questions promptly and seemed mentally hazy. She took insulin during the three days before admission, varying from 5 to 10 units a dose.

1. Barkman, A.: De l'anosognosie dans hemiplégie cérébrale: Contribution clinique à l'étude de ce symptôme, Acta med. Scandinav. **52**:213-254, 1925.

2. Von Hagen, K. O., and Ives, E. R.: Two Autopsied Cases of Anosognosia, Bull. Los Angeles Neurol. Soc. **4**:41-44 (March) 1939.

A most significant point in the personal history was the fact that the patient had been a schoolteacher for many years and after her husband's death succeeded him as principal in the school where she taught. Another point of special interest was that she was at first left handed but later became right handed through training.

The temperature, pulse rate and respirations were normal; the blood pressure was 162 systolic and 80 diastolic. The heart was enlarged, and there was an occasional premature beat. The aortic sound was accentuated.

The patient lay in bed and used only the left extremities; the right side appeared paralyzed. She cooperated well for examination. There was no asymmetry of the face and no deviation of the tongue. The right arm and leg were flaccid. The leg was not moved at all, and voluntary motion of the arm was difficult. The sensations of touch, pressure and pain seemed intact. There was no reflex grasping and the deep reflexes were diminished on the right as compared with the left, consistent with a recent motor cortical lesion. The position sense seemed to be lost on the right, but this is questionable in view of some autotopagnosia. No pathologic reflexes were elicited. The diagnosis of diabetes was confirmed by repeated urinalysis. The blood count was normal, and the blood Wassermann test was negative.

The patient was first seen by one of us (C. W. O.) March 31. At that time she talked with some difficulty but seemed to understand fairly well. She could not read very well but recognized isolated words and figures. She could not write although she could spell. She said she could walk and could move the right leg, but that it didn't work like it should because of "neuritis." She was able to name most objects and some colors, and she could identify colors and objects, even when unable to name them promptly. She could not calculate or copy simple drawings, yet she was able to copy simple construction with two disks, always placing hers in the same relation as in the pattern given. She could not find her right thumb but was consistently correct in distinguishing right from left and in finding the left thumb. However, she was unable to find the left little finger. She could not put out her tongue. The paralysis was least in the face and most in the leg.

In summary, there were anosognosia, agraphia, acalculia and partial finger agnosia but no confusion of right and left. This syndrome corresponded clinically to infarction of the left cerebrum with three areas of necrosis, namely, one in the upper precentral area, one in the left angular gyrus and a third lesion, deep in the left thalamoparietal region, postulated to account for anosognosia. The sensory function was inconsistent with a thalamic lesion. Although right homonymous hemianopia could not be proved, it was diagnosed because the patient consistently bisected a vertical line correctly and almost invariably bisected a horizontal line incorrectly, making the left division much smaller than the right.

A reexamination on April 3 (by C. W. O.) was recorded as follows:

Question	Answer
"What's that on your finger?"	"A ring."
"On what finger is it?"	"The index finger."
"On what finger should the ring be?"	"Index finger."
"Show me the ring finger on the left hand."	(Patient indicated it correctly with her left thumb.)
"Show me my right hand."	(Correctly shown.)
"Show me my thumb."	(Correctly shown.)
"Find your left thumb."	(Correctly shown.)
"Find your right thumb."	(Unable to do so; confused, poor effort.)

The tests for hemianopia were inconclusive, but right homonymous hemianopia was again postulated.

Asked to write "Los Angeles," she said, "Let's see. That's L-o-s. Let me see, I want to make . . . What is that there?" She had made an unintelligible mark near the left hand margin of the paper. She recognized the following colors: purple with hesitation, green promptly, yellow promptly, and for blue she said, "That's blue; that's green." Asked "Is it pink?" she said, "It isn't pink." "Is it green?" "A bright green." "Is it blue?" "That is blue." She again bisected a vertical line correctly and "bisected" a horizontal line so that the right hand portion was much larger than the left. When she was shown a circle and asked to find the center, she indicated a point very close to the left rim. This suggested geometric agnosia as well as hemianopia.

For the calculation "six times six," she repeated "six times six" several times but gave no answer. When "forty-two" was proposed she said, "No." When "thirty-six" was proposed, she nodded her head. For "six plus six," she answered "nine" and seemed satisfied. For "six minus six," she answered, "I don't know what you mean." The examiner said, "I mean 'nothing.'" She answered with a smile, "Six from six leaves nothing." Asked to locate Constantinople, she said, "Can I spell it? C-o-n-t . . ." "No, where is it?" "Ah, you mean what part of the world. It's over in Europe." She spelled "house" and "horse," correctly. Shown her right hand, she said, "That's my left hand." Shown her thumb, she said, "That's my thumb." Shown her ring finger, she said, "That's my index finger." The patient showed some confusion of left and right.

Examination on April 4 (by C. W. O.) showed the patient able to read "HITLER NOT TO" and also the word "GERMANY" from a newspaper headline with very little hesitation. The family found her more alert and rather inclined to worry about her business affairs. Earlier in the illness she had seemed quite happy. On April 5 the patient failed to identify the ring finger on the right hand and showed the index finger consistently although she had a ring on the ring finger at the time.

A study was made in the forenoon of April 6 (by C. R.), with notations as follows: In recognizing and naming objects there was no agnosia for key, pencil, ring, wrist watch and glass. In reading headlines there was no alexia. "ITALY (ITALIAN) TROOPS SEIZES (SEIZE) ALBIA (ALBANIA). POLAND ACCEPTS BRITISH PACT. DUCE STARTS PROTRECTORATE (PROTECTORATE)." When examined for memory, she remembered the headline, "POLAND ACCEPTS BRITISH PACT." Asked when she was born, she was perseverating and unable to recall. She was able to repeat and understand well. She did no spontaneous writing. Asked to write her name, she wrote (approximately) "m." Asked to write from dictation "I am better," her performance was (approximately) "PB31300." Asked to copy figures, "1 2 3," she wrote "3 3." Asked "How much is six times six?" she answered, after perseverating, "twelve." The answer to "four divided by four" was, after perseverating, "six." The problem of "five minus three" was solved by counting fingers. It was concluded that the aphasia was predominantly agraphic.

After the examination the patient ate her lunch as usual. A little later she suddenly had a cold sweat with a brief convulsion. She was cyanotic, and her respiration was of a sighing type with an imperceptible pulse. The blood pressure was 95 systolic and 30 diastolic. Treatment for shock proved temporarily successful, but another brief convulsion occurred, and she died, presumably from coronary occlusion.

Autopsy was performed by Dr. Roland H. Osborne. He observed moderate sclerosis and narrowing of the coronary arteries and both old and recent infarctions at the apical portion of the left ventricle. The only other significant observation was chronic glomerulonephritis.

The brain was examined by Dr. Cyril B. Courville. The arteries at the base were definitely sclerotic. Palpation of the cortex revealed several softened convolutions. The principal area of softening was just caudal to the angular gyrus of the left hemisphere. There were also recent softening of the upper part of the left motor cortex and several small foci in the cerebral cortex on the right side. Multiple yellowish discolorations were noted in the centra of both hemispheres, and the left caudate nucleus showed softening of its head. These softenings were attributed to vascular occlusions, probably embolic.

COMMENT

The gradual impairment of memory may have been connected with the multiple areas of softening throughout the hemispheres. The two foci of particular interest were the one in the region behind the left angular gyrus and the one affecting the upper part of the left precentral gyrus. These two softenings must be regarded as the lesions responsible for the right-sided hemiplegia with crural dominance and Gerstmann's syndrome, of which agraphia was but one symptom.

The interparietal region, which includes the lower portion of the superior parietal lobule and the upper part of the inferior parietal lobule (the angular and the supramarginal gyri), is regarded as important for the concept of the body image. The major softening occurred in this area. In many instances anosognosia (imperception of hemiplegia) has been associated with a thalamic lesion, but such an association was not demonstrated in this case. The thalamic lesion determined hemiplegia and hemianesthesia as well as imperception of the hemiplegia. In our case the paralysis resulted from softening of the motor area, and the failure to perceive it occurred as a result of an interparietal lesion.

Autotopagnosia, disturbance of the concept of the body scheme or image, results from lesions of the thalamoparietal peduncle or of the cortex bordering on the interparietal sulcus, especially the angular gyrus. It occurs in two main forms, depending on the side of the brain which the lesion affects. If the minor hemisphere is involved, amnesia for the minor side of the body develops, while if the major side is affected, the patient has as a rule disturbance of orientation for right and left, finger agnosia, acalculia and agraphia (Gerstmann's syndrome).[3]

Nielsen makes a distinction between anosognosia with anesthesia of the paralyzed parts and anosognosia with amnesia for the paralyzed side. Our patient recognized her paralysis imperfectly, in so far as she had imperfect conception of the body image. She simply did not know whether she had paralysis or not but did know that she was somehow disabled. Anosognosia of Babinski depends on failure of sensory impulses to reach consciousness. With amnesia for a part of the body,

3. Nielsen, J. M.: Gerstmann Syndrome: Finger Agnosia, Agraphia, Confusion of Right and Left and Acalculia; Comparison of This Syndrome with Disturbance of Body Scheme Resulting from Lesions of the Right Side of the Brain, Arch. Neurol. & Psychiat. **39**:536-559 (March) 1938.

it is entirely irrelevant whether that side happens to be paralyzed or not. An understanding of this fact makes it possible to avoid the erroneous diagnosis of a thalamic lesion, or even of a deeply situated lesion of the white matter cutting the fibers between the thalamus and the sensory cortex as described by Von Hagen and Ives.[2]

In a patient who is born left handed but who has acquired a right-handed habit, a parietal lesion might well be expected to produce atypical results. If the patient is, as ours was, well educated, alert and eager to cooperate, the observations become of great interest.

We feel that in this case the lesion of the left upper precentral gyrus produced right hemiplegia with crural dominance. The lesion of the left parietal lobe produced an incomplete Gerstmann's syndrome and also incomplete anosognosia, in that the right hemiplegia was not recognized adequately by the patient. The case illustrates the possibility of localizing with fair accuracy two isolated cortical lesions in one cerebral hemisphere. It also shows how the combined effect of two cortical lesions may roughly but not exactly simulate the effect of a single lesion more deeply placed.

CONCLUSIONS

Anosognosia (imperception of hemiplegia) may arise in three distinct situations:

1. A lesion of the (right) thalamus, causing hemiplegia and hemianesthesia.
2. A lesion of the (right) thalamoparietal peduncle, causing hemiplegia and amnesia for the paralyzed side (hemiamnesia).
3. A combination of a motor cortical lesion and an interparietal lesion, one causing paralysis, the other amnesia for the affected side of the body.

SUMMARY

A case of anosognosia is presented. The paralysis resulted from a lesion of the motor cortex. The imperception of the paralysis is explained by a lesion of the interparietal region (angular gyrus) causing autotopagnosia.

News and Comment

ASSOCIATION FOR ADVANCEMENT OF PSYCHOANALYSIS

The Association for the Advancement of Psychoanalysis was founded in May 1941 by a group of psychiatrists in New York city, with six charter members from other cities. The new organization was deemed necessary to advance the science of psychoanalysis in a spirit of free inquiry, tolerance and openmindedness on the foundation laid by the basic discoveries of Sigmund Freud. In addition to promoting scientific advancement, it seeks to acquaint professional groups whose members deal with human beings and human problems with psychoanalytic concepts for use as tools in their special fields of work, and to serve the public by increasing the general understanding of mental phenomena.

The constitution of the Association states as its functions "(1) to foster the training of psychiatrists in psychoanalytic therapy; (2) to disseminate to the community those elements in psychoanalysis which may be useful to it."

The training program will be carried out through the American Institute for Psychoanalysis. Its facilities include personal analysis, supervised clinical work, seminars and lectures for psychiatrists who wish to become psychoanalysts. Lectures and seminars at the New York Medical College by members of the Association also will be open to physicians and medical students who wish to have knowledge of the contribution psychoanalysis can make toward better understanding of the relation between physician and patient, and between organic and psychic disturbaces. Other evening lectures and seminars at the New School for Social Research invite the attendance of social scientists, clergymen, lawyers, teachers, social workers, nurses, personnel directors and specialists in related fields.

The Association elected Dr. William V. Silverberg, practicing psychoanalyst, associate in psychiatry and chief of the Mental Hygiene Clinic, Lebanon Hospital, as president. Dr. Karen Horney, practicing psychoanalyst, lecturer and author of "The Neurotic Personality in Our Time" and "New Ways in Psychoanalysis," was elected dean of the Institute. Information about the courses to be offered can be obtained from Dr. Harold Kelman, secretary, 1230 Park Avenue, New York.

AMERICAN BOARD OF NEUROLOGICAL SURGERY

The dates for the next examination of the American Board of Neurological Surgery are Oct. 31 and Nov. 1, 1941.

Obituaries

CORNELIS WINKLER, M.D.

1855-1941

On May 8 Dr. Cornelis Winkler, emeritus professor of psychiatry and neuropathology of the Universities of Amsterdam and Utrecht, passed away, at the age of 86 years. Winkler was a historic figure, in the eyes not only of the present generation of Dutch neurologists, most of whom have been his pupils, but also of neurologists in other parts of Europe and elsewhere. After having finished his studies at the University of Utrecht, where Donder was among his teachers, Winkler started his teaching career as a lecturer of psychiatry and neurology in 1885 at his alma mater, where his position was turned into a professorship in 1893. However, as his teaching and working conditions at Utrecht at that time were entirely insufficient, he resigned in 1895 to accept in 1896 a professorship of neurology and psychiatry at the University of Amsterdam, where better conditions existed for these branches of medical science, just separated from internal medicine. Winkler thus was the first in Netherlands to devote himself to neurology and psychiatry only. It was here that, among other researches, he did his excellent work on dermatomeria, which attracted many other Dutch students (Coenen, Langelaan, van Rijnbeck, Dusser de Barenne and S. de Boer) to this subject. Also, his studies on the eighth nerve were done at Amsterdam. In 1915 Winkler left Amsterdam to return to Utrecht, where in the meantime Professor Heilbronner, who died that year, had succeeded in making an up-to-date neurologic and psychiatric clinic. He kept this position until his seventieth birthday, in 1925, and stayed at Utrecht until his death, continuing to work more than ten years, in collaboration with Mrs. Winkler. Winkler's chief interest was always in neurology. He loved to examine the substratum of neural functions in normal as well as in pathologic conditions. A large series of contributions to neuropathology and neuroanatomy appeared from his hand, culminating in the well known guides to experimental researches on the rabbit and the cat brain, published together with his assistant Dr. Ada Potter, and his "Manuel de neurologie," and "Anatomie du système nerveux," a masterpiece in five volumes, printed also in Dutch, the first volume of which appeared at the twenty-fifth anniversary of his professorship, in 1918, and the last, dealing with the striate body and the diencephalon, in 1933. At the twenty-fifth anniversary of his professorship the numerous con-

tributions to neurology and psychiatry previously published in Dutch were republished in English, French and German translations, in seven volumes.

It need not be said that a man with such a vivid interest in his science, and such an excellent teacher besides, exercised a great influence on his students. In addition to those already mentioned, whose work was strongly influenced by him, many among the present Dutch neurologists have been his assistants or have worked in his laboratory, inspired by his activity. Dr. K. H. Bouman, his successor at the University of Amsterdam, was his assistant for many years, and so was Dr. W. M. van der Scheer, now professor of neurology and psychiatry at Gröningen, Germany. Dr. B. Brouwer, professor of neurology at Amsterdam, wrote his thesis in Winkler's laboratory, while as a student I worked with him on the ontogenetic development of the nerve sheaths, before joining the staff of Edinger's institute at Frankfort on the Main. Professor Winkler, together with the late Dutch anatomist Bolk, was also instrumental in creating the Central Institute for Brain-research at Amsterdam, in 1908, the result of an interacademic plan to favor neurologic and neuropathologic studies. All his life he remained a president curator of this institute, and he always favored its interests. Besides, he was the president of the Remmert Adriaan Laan Foundation, an institution created by a Dutch Maecenas for the promotion of neurologic science. The foundation, which grants subventions to Dutch and foreign scientists who wish to work in Netherlands, has attracted several foreign scientists to his laboratory. Until the last years of his life Winkler's interest in neurology remained vivid, as appears from the fact that in 1938 he still gave a lecture at the Academy of Sciences and before the Neurological Society of Amsterdam.

Mrs. E. Winkler-Junius, his second wife, shared his interest and worked with him during more than thirty-five years. While Mrs. Winkler devoted her time more especially to the pathology of the glia, and less to fiber connections, their collaboration was not less valuable than that of the Dejerine-Klümpke couple, in Paris. Winkler's pupils will keep in grateful memory his vivid interest, his never-relaxing energy and his wide erudition. He will remain forever the historic figure in the development of neurology in Netherlands, the man who opened the eyes of Dutch neurologists to problems in this field and who never failed to stimulate their interest and to improve their working conditions.

C. U. Ariëns Kappers.

Abstracts from Current Literature

Anatomy and Embryology

THE EFFERENT FIBERS OF THE THALAMUS OF MACACUS RHESUS: II. THE ANTERIOR NUCLEI, MEDIAL NUCLEI, PULVINAR, AND ADDITIONAL STUDIES ON THE VENTRAL NUCLEI. RICHARD L. CROUCH, J. Comp. Neurol. **72**:177 (Feb.) 1940.

Electrolytic lesions were made in the thalamus of monkeys by means of the Horsley-Clarke instrument. Two weeks later the animals were killed and the brains prepared by the Marchi technic. Lesions were made in the anterior nuclei of 10 monkeys. In no case could fibers be traced to the cerebral cortex. A total of eight lesions were produced in the nucleus medialis dorsalis. There was no degeneration of fibers going to the cerebral cortex from this area. Degenerated fibers from the centrum medianum were seen to spread out in a fanlike manner to adjoining lateral and ventral nuclei and to the centrum medianum of the opposite side. Lesions were placed in the anterior ventral nucleus of 3 monkeys. Masses of fibers from this area passed to the whole extent of the precentral gyrus, and large numbers of fibers went to the superior and inferior frontal gyri. When the lesion was in the nucleus ventralis posterolateralis, efferent fibers were seen to pass to the upper two thirds of the precentral gyrus and to the adjacent portion of the postcentral gyrus. Lesions were placed in the pulvinar of 3 animals. Fibers from these lesions went to the superior colliculus and seemed to terminate in the second and third layers. Other fibers extended into the tegmentum. Still other fibers went to the caudal portion of the superior temporal gyrus. In 1 case fibers went to the upper portion of the angular gyrus and to the posterior parietal gyrus also. Crouch believes that the majority of efferent fibers from the anterior and dorsomedial nuclei are unmyelinated.

ADDISON, Philadelphia.

THE NUCLEAR MASSES IN THE CERVICAL SPINAL CORD OF MACACA MULATTA. ADRIAN F. REED, J. Comp. Neurol. **72**:187 (Feb.) 1940.

The purpose of this investigation was to localize the columns of cells which give rise to the motor components of the nerves of the brachial plexus of Macaca mulatta. Nine animals were used in the experiments. In each case a piece about 2.5 cm. long was excised from a selected nerve of the brachial plexus. Thirteen to seventeen days later the animals were killed and the spinal cords prepared to show Nissl substance. Dissections were made to determine the distribution of the nerves from which the piece had been excised. Reed distinguished five fairly distinct groups of motor cells in the ventral horn of the spinal cord. Four were present from the third cervical through the first thoracic segment. Three groups were seen in the first and second cervical segments. In the sixth and seventh cervical segments a fifth group was present. The lateral horn cells were demonstrated only in the lateral horn of the first thoracic segment. By studying the chromatolysis of the motor cells in the different experimental animals, Reed was able to identify the location of the cell groups and columns from which originated each component of the brachial plexus.

FRASER, Philadelphia.

STUDIES ON THE DIENCEPHALON OF THE VIRGINIA OPOSSUM: II. THE FIBER CONNECTIONS IN NORMAL AND EXPERIMENTAL MATERIAL. DAVID BODIAN, J. Comp. Neurol. **72**:207 (April) 1940.

In addition to normal series of brains of the opossum prepared by myelin or reduced silver methods, 6 brains were prepared by the Marchi technic after lesions

had been produced in the parietal area of the cortex and the underlying diencephalon. From the normal material Bodian has already described the nuclear configuration and the fiber tracts of the diencephalon of the opossum. Here he considers in detail the fiber systems, especially those which are least clear. The dorsal thalamus is markedly primitive, as compared with that of more specialized mammalian brains, especially in the great development of the dorsal thalamic commissures. The hypothalamus shows a higher degree of specialization than any other part of the diencephalon. The medial group of hypothalamic nuclei, which includes the mamillary bodies, has widespread descending connections with the tegmentum by way of the related hypothalamotegmental and mamillotegmental tracts and the associated olfactotegmental bundles. The tectothalamic and thalamotectal connections are well developed, as is characteristic of primitive brains. Bodian includes over fifty nuclei, thirty tracts and ten commissures in his discussion of the complex connections of the diencephalon.

ADDISON, Philadelphia.

THE CEREBRAL CORTEX IN SOME TINAMIDAE. E. HORNE CRAIGIE, J. Comp. Neurol. **72**:299 (April) 1940.

The brains of 6 species from the little known order of Tinamiformes were studied. The tinamou is a primitive bird related to the ostrich. Craigie describes the cerebral hemispheres of these birds, especially the cerebral cortex, and compares the latter with that of other birds he has studied. The cerebral hemispheres, the cortex in particular, resemble those of ratite birds. The parts examined were in general similar in all the species of Tinamidae studied, except in Rhynchotus, in which the olfactory bulbs are much reduced and fused, as in the sparrow. The resemblance of the cortex in the tinamou to that in ratite birds is in keeping with their inclusion in a single group, the Palaeognathae.

ADDISON, Philadelphia.

THE STRUCTURAL ORGANIZATION OF THE INFERIOR MESENTERIC GANGLIA. ALBERT KUNTZ, J. Comp. Neurol. **72**:371 (April) 1940.

The material studied was obtained from preparations of human inferior mesenteric ganglia or from the inferior mesenteric ganglia and associated nerves of normal and experimental cats. The experimental animals were subjected to three main operative procedures: (1) The lumbar segments of both sympathetic trunks were extirpated and the intermesenteric nerves divided in order to insure interruption of all preganglionic fibers to the inferior mesenteric ganglia; (2) in most of these animals the hypogastric nerves also were interrupted, and the plexus on the lumbar portion of the aorta was removed as completely as possible; (3) two or more colonic branches of the inferior mesenteric artery with the nerves accompanying them to the colon were divided. The animals were killed after three weeks. All material was prepared by a Cajal silver technic. The results suggest that the inferior mesenteric ganglia, like the celiac ganglia previously described by Kuntz, are more complex in their structural organization than the ganglia of the sympathetic trunk. Most of the cells of the inferior mesenteric ganglia appear to be synaptically related to preganglionic spinal nerve fibers and thus constitute peripheral links in visceral efferent conduction pathways. After degeneration of the lumbar splanchnic and intermesenteric nerves some synaptic connections in the inferior mesenteric ganglia persisted, which indicates that these ganglion cells are synaptically related to certain axons which are not spinal nerve components. Intact fibers existed in the distal portions of colonic nerves after degeneration of the fibers which extended distalward from the inferior mesenteric plexus after section of the colonic nerves. This supports the assumption that axons of enteric ganglion cells extend centralward in the colonic nerves and gives a demonstrable basis for reflex arcs with synaptic connections in the inferior mesenteric ganglia.

FRASER, Philadelphia.

A Comparative Fiber and Numerical Analysis of the Pyramidal Tract. A. M. Lassek and G. L. Rasmussen, J. Comp. Neurol. **72**:417 (April) 1940.

Lassek and Rasmussen studied the pyramidal tract in eight species—opossum, mouse, rat, rabbit, cow, cat, dog and man. Its most constant characteristic was the decussation in the lower portion of the medulla, and therefore the region selected for study was just rostral to the decussation. The material was sectioned transversely and stained by Davenport's method for silver impregnation on the slide. Total counts of axons were made and the diameters of the stained axons measured. Shrinkage was determined and values adjusted accordingly. All fibers in the tract were counted in the mouse, and one quarter of those in the tracts of the other species, except in the tract of man, in which counts were made on one eighth and one sixteenth of the cross sectional area. The approximate numbers of fibers computed to be present at the level counted were as follows: man 1,101,000, dog 285,300, cat 186,000, rabbit 101,700, opossum 75,700, rat 73,000 and mouse 32,300. The number in the pyramidal tract of the cow was estimated at 500,000. The areas, expressed in square millimeters, of the tract at this level were: man 11.4, dog 3.5, cat 1.1, rabbit 0.28, opossum 0.28, rat 0.3 and mouse 0.067. Man possessed the largest fibers in the series. These were between 10 and 25 microns and constituted about 4 per cent of the total, or 40,000. About 96 per cent of the fibers were smaller than 10 microns, and most of these were between 1 and 5 microns. The fibers of the pyramidal tract of the cow were extremely small, but more of them were myelinated than in the smaller animals. The cat differed from man and dog in that it possessed no large fibers. The smaller animals showed a relatively large number of cells and a greater number of fibers per unit area.

Addison, Philadelphia.

The Excitable Cortex in Perameles, Sarcophilus, Dasyurus, Trichosurus and Wallabia (Macropus). A. A. Abbie, J. Comp. Neurol. **72**:469 (June) 1940.

Abbie described the situation, extent and structure of the excitable cortex in a series of 28 marsupials, of which 2 were pouch embryos and the others adults. Most of the animals were stimulated by bipolar induction while under ether anesthesia. At the conclusion of each experiment the animal was killed with chloroform, the brain was removed and blocks were cut to include the excitable cortex. The area of excitability was located in the region of the orbital sulcus. In Perameles the head area was rostral to the arm area. In Sarcophilus and Dasyurus the head area was ventral to the arm area. In these three forms there was no response in the posterior limbs. In Trichosurus and Wallabia the head area was rostral and the leg area posterior to the arm area. The excitable area was characterized by the possession of a definite fourth lamina. In Perameles, Sarcophilus and Dasyurus the fourth lamina was composed of cells of medium size. In Trichosurus and Wallabia the cells of the fourth lamina were smaller and approached the specifications of an "internal granular" lamina.

Fraser, Philadelphia.

Comparison of the Changes Caused by Fatigue and by Aging in the Cerebral Cortex of Mice. Warren Andrew and Nancy Valérie Andrew, J. Comp. Neurol. **72**:525 (June) 1940.

Black mice of the following ages were studied: 2 each of 23, 25, 43, 46, 98, 101 and 290 days; 1 of 744 days, and 3 of 746 days. Sections were stained for Nissl substance. One animal in each age group was fatigued to exhaustion, and the other served as a control. Fifty cells of each brain were classified as to the amount of Nissl substance, the staining properties of the nucleus and the number of satellite cells in contact with the nerve cell body. The only localization of the cells studied was obtained by beginning observation in the layers of pyramidal and

of polymorphic cells in the cerebral cortex at a point just above the anterior end of the cornu ammonis and by proceeding forward from there. No consistent differences between the cells were found when fresh and fatigued animals of the same age were compared. There were definite changes in the cells of the cerebral cortex with age. They consisted chiefly in loss of Nissl material, an increased degree of satellitosis and a tendency to amitotic division of the nucleus of the nerve cell.

ADDISON, Philadelphia.

ON THE CONTROL OF GROWTH AND ACTIVITY OF THE PARS INTERMEDIA OF THE PITUITARY BY THE HYPOTHALAMUS IN THE TADPOLE. WILLIAM ETKIN, J. Exper. Zool. **86**:113 (Feb.) 1941.

It had previously been found that transplantation of the pars intermedia of the pituitary, which is the source of a hormone which induces expansion of melanophores, into hypophysectomized amphibian hosts causes the development of extremely black pigmentation, instead of merely a return to normal pigmentation. In order to elucidate this phenomenon, grafts of the epithelial pituitary as a primordium or as a differentiated gland were made in several species of normal and of hypophysectomized Rana tadpoles. Successful grafts led to excessive pigmentation of the host in all cases. The pars intermedia of such a graft was much larger than that of the control normal gland in the same animal and showed cellular hypertrophy with increased basophilia. Similar changes in pigmentation and in the pars intermedia of the pituitary in situ followed partial destruction of the infundibulum. It is concluded that growth and functional activity of the pars intermedia are normally restrained by the infundibulum, probably through the mediation of hypothalamic-hypophysial nerve pathways.

WYMAN, Boston.

Physiology and Biochemistry

CLINICAL STUDIES OF EXPERIMENTAL HUMAN VITAMIN B COMPLEX DEFICIENCY. K. O. ELSOM, F. H. LEWY and G. W. HEUBLEIN, Am. J. M. Sc. **200**:757 (Dec.) 1940.

Elsom, Lewy and Heublein report the results of repeated clinical examinations and studies of cardiovascular, neurologic and hematopoietic functions and of alterations in the roentgenographic appearance of the gastrointestinal tract in a subject while receiving a deficient diet alone and also following the addition to the diet of thiamine hydrochloride, riboflavin and brewers' yeast. The subject was a healthy woman aged 60 who voluntarily consumed a constant daily quantity of a weighed diet which was adequate in everything except the vitamin B complex. The experiment was divided into five consecutive periods: (1) the first week on the deficient diet, or the control period; (2) the subsequent eight weeks, in which deficiency developed; (3) eighteen days, when thiamine hydrochloride was added to the diet in doses ranging from 20 to 120 mg. daily; (4) twenty days, during which riboflavin, 6 mg. daily, was administered in addition to thiamine hydrochloride, and (5) a final eighteen days, when brewers' yeast alone, 42 Gm. daily, was given. The subject was examined daily and the symptoms and physical signs recorded. After five weeks on the experimental diet the subject complained of dyspnea and palpitation. All the cardiovascular symptoms and physical signs regressed after the administration of thiamine hydrochloride. Mild anorexia was present after the subject had been on the diet one week and ultimately became extreme. Appetite returned promptly after the administration of thiamine hydrochloride. Roentgen examination of the gastrointestinal tract at the end of the period of deficiency showed no abnormality except for some increased caliber of the jejunal loops. Three days after beginning the experimental diet

diminution in electric irritability of the peripheral nerves and some disturbance of sensations were observed. Four days following the administration of thiamine hydrochloride all neurologic symptoms and signs had disappeared except for electric underexcitability. Mental symptoms formed a striking part of the clinical picture. During the fifth week of deficiency the subject first complained of nervousness and irritability, which gradually increased in severity. These symptoms were not entirely relieved until yeast was added to the diet. Excessive fatigability was noticed and ultimately became extreme. Edema of the upper and lower extremities, present by the end of the first week, slowly increased. Mild macrocytic anemia developed during the period of deficiency, which was uninfluenced by thiamine hydrochloride or riboflavin but was relieved after the subject had received a general diet and brewers' yeast for four weeks. Inasmuch as identical experiments were carried out in 1933, it was possible to compare the manifestations of induced deficiency. In 1933, however, glossitis and neurologic abnormalities were prominent, while in 1938, though present, they were comparatively mild. The symptoms and physical signs in the present study were comparable to those observed in the same subject in 1933, although certain differences are described.

MICHAELS, Boston.

PRELIMINARY ANALYSIS OF GROUPING BEHAVIOR IN PATIENTS WITH CEREBRAL INJURY BY THE METHOD OF EQUIVALENT AND NON-EQUIVALENT STIMULI. WARD C. HALSTEAD, Am. J. Psychiat. **96**:1263, 1940.

Halstead studied 11 normal persons and 26 neurosurgical patients, 12 of whom had lesions of one frontal lobe and 14 lesions of the brain posterior to the frontal lobes. The method of study consisted in placing sixty-two objects varying in their objective properties in a predetermined manner on a table before the subject and then testing for (1) range of interest and familiarity, (2) spontaneous grouping of objects, (3) recall of test objects by the method of imminent recall, (4) nominal equivalence and (5) the basis of equivalence of the test objects in groups.

Halstead found the greatest deviation from normal in persons with a unilateral lesion of the frontal lobe. He points out that it remains to be seen whether the grouping behavior of patients with lesions of the frontal lobe is characteristic.

FORSTER, New Haven, Conn.

A NOTE ON THE USELESSNESS OF ANALEPTIC DRUGS COMBINED WITH LUMINAL IN THE TREATMENT OF EPILEPSY. T. T. STONE, I. FINKELMAN and A. J. ARIEFF, Am. J. Psychiat. **96**:1377, 1940.

Stone, Finkelman and Arieff used analeptic drugs, such as coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamide), amphetamine, metrazol and ephedrine, in anticonvulsant therapy and studied the effects of these agents with reference to (1) allaying unpleasant symptoms from the anticonvulsant drugs, (2) allowing use of increased doses of the anticonvulsants and (3) increasing the number of seizures. The authors found that toxic symptoms were not allayed and that therefore no increase in dosage of the anticonvulsants was possible. No significant change in the number of seizures was noted.

FORSTER, New Haven, Conn.

BIOELECTRIC RESPONSES IN METRAZOL AND INSULIN SHOCK. J. E. GOODWIN, W. K. KERR and F. L. LAWSON, Am. J. Psychiat. **96**:1389, 1940.

Goodwin, Kerr and Lawson studied the effects of convulsive doses of metrazol and insulin on the electric activity of the brain of the rabbit and the relation of these responses to physiologic phenomena associated with metrazol and insulin shock. Metrazol was administered either locally or intravenously; insulin was administered subcutaneously. Intravenous injection of metrazol resulted in four electrocortical phases: beginning slow activity, going over into fast activity and

followed by decreased activity and, ultimately, by recovery. These changes were recorded from the cerebral cortex, the thalamus, the midbrain and the lower part of the brain stem.

Local application of metrazol resulted in a change in pattern of the cortical electric activity which was fundamentally the same as that produced by intravenous injection. However, certain areas of the cortex were more vulnerable than others to local application of the drug.

Bioelectric changes were found to be produced not by insulin itself but through hypoglycemia.

The four phases of electrocortical activity produced by administration of metrazol are correlated with the clinical picture of metrazol shock.

FORSTER, New Haven, Conn.

THE EFFECT OF ALCOHOL ON CEREBRAL METABOLISM. WALTER GOLDFARB, KARL M. BOWMAN and JOSEPH WORTIS, Am. J. Psychiat. **97**:384, 1940.

Goldfarb, Bowman and Wortis studied the femoral arterial and the internal jugular venous bloods of 10 acutely intoxicated patients. Studies were made during the intoxicated period and again on recovery. The authors found decreased oxygen uptake in 6 patients during the intoxicated period. During recovery all 10 patients had normal oxygen uptakes. No conclusions could be drawn as to dextrose uptake. The carbon dioxide content of the venous blood was uniformly lower during intoxication. The authors point out that the depressant effect of alcohol may be due to decreased oxygen metabolism of the cortex.

FORSTER, New Haven, Conn.

HUMAN BRAIN METABOLISM: NORMAL VALUES AND VALUES IN CERTAIN CLINICAL STATES. JOSEPH WORTIS, KARL BOWMAN and WALTER GOLDFARB, Am. J. Psychiat. **97**:552, 1940.

Wortis, Bowman and Goldfarb studied metabolism of the brain by determining values for oxygen, carbon dioxide, dextrose and lactic acid in both arterial and internal jugular venous blood. The circulation time was determined by injection of cyanide. The authors first determined the values for normal subjects and compared these with similar observations on patients with certain clinical states. Untreated schizophrenic patients showed no deviation from the normal group. After insulin therapy, however, a drop in dextrose uptake and an increase in the carbon dioxide of jugular venous blood were observed. In 14 patients with senile arteriosclerosis a normal oxygen uptake was found, despite a decreased oxygen content of arterial blood. There was a slight increase in the circulation time in this group. No significant difference was found in patients with dementia paralytica. In 52 patients with chronic alcoholism, after the effects of the debauch had receded, both the dextrose and the oxygen uptakes were increased. In patients with acute alcoholism the oxygen uptake was diminished during intoxication and both arterial and jugular venous carbon dioxide tensions were diminished. Paraldehyde was found to increase oxygen uptake and circulation time, while morphine decreased both.

FORSTER, New Haven, Conn.

OXYGEN CONSUMPTION IN THE PSYCHOSES OF THE SENIUM. D. EWEN CAMERON, HAROLD E. HIMWICH, S. R. ROSEN and JOSEPH FAZEKAS, Am. J. Psychiat. **97**:566, 1940.

Cameron, Himwich, Rosen and Fazekas studied the arterial and internal jugular venous blood and the circulation time of 23 patients with typical senile psychoses. The circulation time was found to be increased and the average oxygen content of arterial blood decreased. The arteriovenous difference for oxygen,

however, was within normal range. The decreased oxygen of arterial blood may be due to pulmonary emphysema, failure of diffusion from the capillaries of the alveolar walls or decreased hemoglobin in the blood. The authors conclude that a normal arteriovenous difference for oxygen in the face of a prolonged circulation time indicates diminished cerebral oxygen consumption.

FORSTER, New Haven, Conn.

WALTZING GUINEA PIGS WITH PARTICULAR REFERENCE TO OCULAR MOVEMENTS AND RIGHTING REFLEXES. DAVID G. COGAN, Arch. Ophth. **24**:78 (July) 1940.

Cogan observed that waltzing guinea pigs when rotated did not show a normal vestibular nystagmus. Normal guinea pigs, like most other animals, show a characteristic nystagmus on rotation. Waltzers, after being rotated, either remain stationary or make nodding movements of the head and irregular movements of the head and body. They show a characteristic and complete absence of labyrinthine control over ocular movements and positions of the eyes, over movements of the heads and positions of the head and over the righting reflexes. Although labyrinthine control is absent in the waltzing guinea pig, the righting reflex is carried on with more or less success by the visual sense and by contact with the ground.

SPAETH, Philadelphia.

FATE OF THIAMINE IN THE DIGESTIVE SECRETIONS. D. MELNICK, W. D. ROBINSON and H. FIELD, J. Biol. Chem. **138**:49, 1941.

When thiamine hydrochloride is taken orally by normal subjects in the post-absorption state, much less is excreted in the urine than when similar amounts are ingested immediately after a meal. This may be due to instability of thiamine hydrochloride in a more alkaline gastrointestinal tract when gastric secretion is at a minimum. Thiamine was found to be stable in normal gastric juice of p_H 1.5 to 8.0 during sixteen hours of incubation. In the presence of antacids, thiamine hydrochloride added to gastric juice may be adsorbed or destroyed during the period of incubation. Neither gastric juice containing hemin nor gastric juice from achlorhydric patients destroys it. Bile and pancreatic juice cause an apparent loss of from 50 to 90 per cent. Since incubation with a yeast enzyme preparation results in the recovery of more thiamine hydrochloride, the true loss varies from 40 to 55 per cent. Because of the presence of food in the stomach, thiamine is retained for longer periods, thus allowing greater absorption and preventing passage into the small intestine, where the vitamin may be destroyed by bile and pancreatic juice.

PAGE, Indianapolis.

THE RELATION OF ATROPHY TO FIBRILLATION IN DENERVATED MUSCLE. D. Y. SOLANDT and J. W. MAGLADERY, Brain **63**:255, 1941.

The fibrillation of denervated muscle was observed electrically by means of the needle electrode. It was found to be unaffected by curare, physostigmine, atropine, potassium chloride or the usual anesthetic and sedative drugs, except in doses which are usually lethal. It could be stopped temporarily by injection of calcium chloride, and for long periods by quinidine.

Since the atrophy of denervated muscle has been attributed to the fatigue resulting from constant fibrillary overactivity, it was felt that by stopping fibrillation the development of atrophy might be retarded.

A normal atrophy curve for the gastrocnemius-soleus muscle group of the denervated rat was determined. When the muscles of similar animals were prevented from fibrillating by the administration of quinidine sulfate, the rate of atrophy was slightly retarded. However, similar delay in atrophy was produced by the administration of soluble barbital U. S. P. (sodium barbital) and for this

reason it was felt that the slight decrease in atrophy which was observed could well be attributed to the sedative effect of the quinidine rather than to its effect on fibrillation. It was concluded that the prevention of fibrillation in denervated muscle by the administration of quinidine sulfate did not retard the development of the atrophy of denervation. The loss in weight of denervated muscle is not due to fibrillary activity.

MASLAND, Philadelphia.

EXPERIMENTAL LESIONS IN THE BASAL GANGLIA OF THE CAT. E. G. T. LIDDELL and C. G. PHILLIPS, Brain **63**:264, 1941.

Electrolytic lesions of the basal ganglia of the cat were produced by means of an Adrian concentric needle, insulated except at the tip and guided into the desired region by use of the Souttar-Beattie sterotaxic apparatus. Lesions were produced in the lenticular, caudate and subthalamic nuclei and the claustrum. The location of the lesion was confirmed histologically. In no instance was there evidence of involvement of the pyramidal tract.

The clinical picture was characteristic in all the animals. The severity of the physical signs is marked at first, then diminishes to a steady level, which is maintained for three months or more. The outstanding feature consists of hypertonia of extensor muscles on the contralateral side. This is most prominent with the animal relaxed. It is plastic and interferes little with ordinary movement. It is associated with a delayed flexor reflex and deficient tactile placing reactions. There may be temporary defective closure of the contralateral eyelid. In addition, there is some flexor hypertonia on the ipsilateral side. The gait may be slightly disturbed, and after a unilateral lesion the animal may tend to circle to the opposite side. Bilateral lesions tend to produce a noticeably stiff gait. The contralateral limb may show an abortive "magnet reaction"; after forced flexion it tends to follow an object placed against the foot pad, but does so for only an inch or so at a time. There was no sign of spontaneous tremor or of other involuntary movements.

MASLAND, Philadelphia.

THE PHYSIOLOGIC ACTION OF THE VITAMIN B COMPLEX. F. H. LEWY, Confinia neurol. **3**:74, 1940.

Lewy states that the various fractions of vitamin B complex act as enzymes and play an important part in the carbohydrate metabolism of plants and animals. He expresses the belief that thiamine is instrumental in the conversion of carbohydrates into fat and that pyruvic acid plays the role of an intermediary in this process. Thiamine and choline have an antagonistic effect on liver fat, and choline seems to be one of the components of nutrition that is responsible for the action of thiamine. Little is known regarding riboflavin deficiency in man, but after decortication of the adrenals or extirpation of the pancreas normal function cannot be restored by administration of adrenal cortex extract or insulin in the absence of riboflavin or thiamine or both. Nicotinic acid must be converted within the body to coenzymes I and II before it can cure pellagra. All the fractions of vitamin B complex are needed in the metabolic and respiratory processes of individual cells; thiamine seems to be needed for the normal function of peripheral and cranial nerves, whereas riboflavin and nicotinic acid, and possibly vitamin B_6, seem to be more important in the metabolism of the central nervous system.

DE JONG, Ann Arbor, Mich.

RELATION OF THE DIENCEPHALON TO MOTILITY. W. R. HESS, Arch. f. d. ges. Physiol. **243**:634, 1940.

The motor symptoms produced by rhythmic electrical stimulation of the various parts of the diencephalon were systematically investigated in cats. The location of the stimulating electrodes was histologically controlled, and the motor effects were recorded by motion pictures. On the eyelids only closure effects, never opening

reactions, were obtained. The primary effect appears in the contralateral eye; an ipsilateral reaction is obtained with increasing voltage after a latent period of up to twelve seconds, which indicates "facilitation." The chief points of stimulation lie on a line that starts at the medial border of the internal capsule and can be traced caudally to the lateral border of Meynert's tract; the line apparently corresponds to a fiber tract, which, however, could not be more clearly defined at present. Further motor effects were observed in the forelegs, the hindlegs and the tail; the areas from which such effects were observed were similarly located as the lid areas, and they overlap each other widely. For the motor effects in the tail higher voltage (above 1.5 volts) is necessary than for the other effects.

SPIEGEL, Philadelphia.

MOTOR EFFECTS ON THE FACE OF STIMULATION OF THE DIENCEPHALON. W. R. HESS, Arch. f. d. ges. Physiol. **243**:678, 1940.

Continuing his stimulation experiments on the diencephalon, Hess studied in detail the effect of such stimulation on the facial muscles. The motor effects observed were rhythmic and corresponded in rate to the stimulating current (8 impulses per second). The points of stimulation lie in the same region as that previously described for the closure effects on the eyelids. They extend, however, at more ventral levels into a region located between the cerebral peduncle and the descending column of the fornix. Stimulation points were also found in the neighborhood of the corpora mamillaria, in the corpus callosum and in the vicinity of the foramen of Monro. With the lowest voltage twitching of the ears and movements of the whiskers appeared. The whiskers were moved backward on the contralateral side and forward on the ipsilateral side. With higher voltage the contralateral part of the upper lip and sometimes also the corresponding cheek were raised. Two types of effects on the nictitating membrane were observed: retraction, as part of a sympathicus effect, and active pushing forward of the membrane over the cornea. The latter reaction is a reflex due to stimulation of the ophthalmic branch of the trigeminus nerve; its efferent pathway is represented by the abducens nerve.

SPIEGEL, Philadelphia.

EXPERIMENTAL CEREBRAL ANEMIA: PRELIMINARY INVESTIGATIONS. B. BJERNER and A. SWENSSON, Acta psychiat. et neurol. **15**:211, 1940.

Bjerner and Swensson state that this is the first communication of a series of studies on cerebral circulation, particularly in its relation to convulsive seizures. A number of rats and rabbits were decapitated at various stages of metrazol convulsions, the brains fixed, sectioned, stained with orthotolidine and compared with normal control brains similarly prepared. Often, though not constantly, generalized cerebral anemia was found to precede or accompany the convulsions. Later patchy areas of hyperemia might be seen, but the anemia could be found even after several convulsions in some animals. The authors recognize the difficulties of drawing valid conclusions about the dynamics of the circulation from such experiments and attempt no general conclusions. They were unable to confirm the presence of localized areas of ischemia which were described by Dresser and Scholz in experimental metrazol convulsions.

BRENNER, Boston.

Psychiatry and Psychopathology

THE PSYCHIATRIC FINDINGS IN THE CASES OF 500 TRAFFIC OFFENDERS AND ACCIDENT-PRONE DRIVERS. LOWELL S. SELLING, Am. J. Psychiat. **97**:68, 1940.

In the group of 500 traffic offenders and accident-prone drivers, Selling found 11 with definite psychoses. The intelligence quotients of the nonpsychotic offenders

were found to range from 31 to 122, with a median of 77. Alcoholism was present in 35.8 per cent of the group. Among the neurotic offenders various mechanisms were found to contribute to the offense. Selling states that neurotic drivers do not represent a serious threat, as their insight is preserved, but that persons with major psychoses do, because insight is impaired. Selling stresses the importance of psychiatric examination for the latter group of persons. The question of reissuing operators' licenses to psychotic persons whose illnesses are in remission should be considered individually.

FORSTER, New Haven, Conn.

A SURVEY OF MENTAL ILLNESS ASSOCIATED WITH PREGNANCY AND CHILDBIRTH. JOHN L. SMALLDON, Am. J. Psychiat. **97**:80, 1940.

Smalldon studied the records of 220 women suffering from psychoses associated with childbirth and the puerperium. One hundred and seven of the group had manic-depressive psychosis and 64 schizophrenia. The psychoses of 8 patients were diagnosed as toxic-exhaustive. A greater prevalence of such disorders was found among Jewish patients; heredity was of most importance in the group with manic-depressive psychoses. The prepsychotic personality coincided with the type of illness. Among the manic-depressive patients important mechanisms were hostility to the newborn child and ambivalence toward the husband and child. Father fixation was found not to be especially prevalent among the schizophrenic patients. Guilt reactions were prominent. Smalldon states that there is no distinction between these patients with psychoses associated with the puerperium and those with nonpuerperal psychoses.

FORSTER, New Haven, Conn.

A STUDY OF INSIGHT OF PSYCHIATRIC PATIENTS. CARROLL W. OSGOOD, Am. J. Psychiat. **97**:152, 1940.

Osgood studied 100 hospitalized psychiatric patients with respect to the quality and degree of insight. The patients were grouped on the basis of insight, as follows: (1) none, (2) slight, (3) fair and (4) good. Sixty per cent of the depressed patients had fair or good insight on admission, as compared with only 23 per cent of the patients with all other types of mental illness studied. All of the psychoneurotic patients had fair insight or better. Osgood found that on discharge all but 1 of the patients who had recovered or improved showed good insight. Absence of insight on admission did not militate against the prognosis of recovery. However, partial insight seemed to offer a poorer prognosis. Absence of insight was frequently correlated with such manifestations as disorientation, impaired comprehension, irrelevance, memory involvement and hallucinations.

FORSTER, New Haven, Conn.

EFFECT OF AFFECTIVE STATES ON THE HEART. HANS HERMANN MEYER and FRANZ BILLMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:515 (Nov.) 1940.

One hundred patients with depressions and severe anxiety states were studied electrocardiographically. The ages of the patients ranged from 15 to 45 years; two thirds were females. Thirty-five had schizophrenia; 24, psychopathic personalities; 15, involutional syndromes; 12, manic-depressive reactions, and a few, other mental conditions. The authors conclude that the electrocardiographic findings in this group of psychotic patients were no more abnormal than those of normal control subjects. There are no specific electrocardiographic patterns for any of the psychoses, as other investigators, Ljundberg, for example, have maintained. Emotional disturbances alone do not cause permanent alterations in the heart.

SAVITSKY, New York.

Diseases of the Brain

ACUTE GENERAL PARESIS [DEMENTIA PARALYTICA]. M. HERMAN and M. P. ROSENBLUM, Am. J. Psychiat. **96**:1311, 1940.

Herman and Rosenblum emphasize the frequency of acute onset in dementia paralytica and divide cases of this kind into four groups: 1. The fulminating type in which the clinical picture is that of an acute delirium with the characteristic neurologic signs of dementia paralytica and a febrile course. A fatal termination may occur in one to three weeks. The associated pathologic condition is a typical, intense meningoencephalitis of necrotic character. 2. The convulsive type in which seizures occur early and may be the first indication of the disease. The course may vary: There may be either an increase in seizures, proceeding to a fatal termination, or the development of the chronic form of dementia paralytica. 3. The catatonic type, which may be difficult to differentiate from catatonic schizophrenia. However, the serologic reactions, the marked mental confusion and the aphasia and apraxia are aids in diagnosis. 4. The acute confusional type. This is the most common of the types of acute onset and consists of clouded states, which may become chronic or, less commonly, develop as a series of clouded episodes with clear intervals over a period preceding the establishment of the chronic state. The authors point out the gravity of the prognosis in cases in which the onset is acute and emphasize the necessity for emergency treatment.

FORSTER, New Haven, Conn.

A REVISION OF THE CEREBELLOPONTILE ANGLE LESION SYNDROME. JULIUS WINSTON, Arch. Otolaryng. **32**:877 (Nov.) 1940.

Winston found that of 16 cases of neural and extraneural unilateral tumors of the cerebellopontile angle, typical signs were present in 59.2 per cent. Findings on the side of the lesion indicate a peripheral and those on the contralateral side a central lesion. In practically all the cases there were (1) a spontaneous nystagmus on looking up, down or straight ahead; (2) a disproportion between the duration of nystagmus and vertigo after turning, and (3) a loss of function of either the vertical semicircular canals or the vertical and horizontal semicircular canals with good hearing on the opposite side. These findings are indicative of a central lesion. In all the cases there was tolerance to vestibular stimulation. In 7 cases of unilateral angle tumor the opposite vertical and horizontal semicircular canals functioned normally, but in these cases there was a spontaneous nystagmus which supplied the central element of the vestibular picture. If the term cerebellopontile angle lesion syndrome should be changed to "evidence of a peripheral lesion on the same side as the cerebellopontile angle lesion in addition to evidence of a central lesion" (the latter evidence not being confined to a loss of function of the opposite vertical semicircular canals), then in 23, or 85.1 per cent, of 27 cases of unilateral angle tumor the condition could be considered as conforming typically with the revised concept of the syndrome associated with a lesion of the cerebellopontile angle. In 6 of the 7 cases of bilateral angle tumor, also, the condition would conform typically to the revised concept. In 1 case of bilateral angle tumor it was not possible to make an examination for spontaneous nystagmus, for the patient was totally deaf and blind. In both cases of extraneural bilateral angle tumor total deafness and blindness were also present, but spontaneous nystagmus could be observed in 1 case when the patient looked straight ahead and in the other case when the patient deviated the eyes to one side or the other. When the group of unilateral and bilateral angle tumors are combined the typical picture might be said to be found in 29 of the 34 cases, or 85.3 per cent. Therefore, if the designation of the syndrome were changed to "evidence of a peripheral lesion on the same side as the cerebellopontile angle lesion in addition to evidence of a central lesion" then in 85.3 per cent of this series, instead of 59.2 per cent, the condition would have conformed to the revised concept of the syndrome.

HUNTER, Philadelphia.

HEAD NOISES. EDMUND P. FOWLER, Arch. Otolaryng. **32**:903 (Nov.) 1940.

Vibratory tinnitus is easily masked; nonvibratory tinnitus is masked with difficulty. The ease of masking nonvibratory tinnitus varies with the locations of the lesions and with the accompanying deafness. An analysis of tinnitus must include a study of the frequency of the tinnitus as well as its intensity. This is preferably done on the opposite ear, owing to the recruitment phenomenon. Note should also be made of its tonal character, constancy, intermittency, reactions to certain physical influences and masking. These points help in the diagnosis of the location of the lesion and in prognosis. If the tinnitus is bilaterally similarly tonal and coincidental in timing and quality it is probably central in origin. Monaural tinnitus may also be central. If the tinnitus is bilaterally unequal in frequency or intensity it may be preserved by the patient in one ear only because of a masking effect. Auditory hallucinations may take on the form of various types of tinnitus. They may arise from any part of the tract, namely, from the cochlea, cochlear nerve, ganglion cells, auditory tracts and protective pathways. They are not necessarily central, and have little or no dependable localizing value in diagnosis. When tinnitus occurs with sharp dips or narrow deep troughs in the audiogram curves its frequency occurs within the limits of the slopes. This suggests that both the tinnitus and the deafness arise from limited lesions in the basilar membrane or/and the associated spiral ganglia. Central lesions probably cause wider bands of deafness and tinnitus. The tinnitus occurs in the irritative phase of the lesion and foreshadows subsequent degeneration of the neural elements involved. When tinnitus occurs with flat audiogram curves it is usually less localized in frequency. Under these conditions it sounds like a roar, machinery, motors or waves. It is then not so apparent that the deafness and the tinnitus arise from the same lesions. It is believed, however, that this is generally the case. There are exceptions to the foregoing general observations. No one has reported hearing tinnitus by the method of Wever and Bray. Most tinnitus is of central origin. The more chronic the tinnitus the less the probability of its cessation with a comparable gain in hearing. In some cases the lesion causing the tinnitus may be in an area with total degeneration, "dead wire" effect, or the subjective noise may occupy the neurons or part of the basilar membrane affected (the "busy line" effect). A thermal noise with flat characteristics was used to measure all frequencies from 128 to 9,000. In the majority of cases the tinnitus fell within these limits. Deafness may occur without head noises, but head noises cannot occur without deafness. Many treatments which are used as so-called cures for deafness appear to improve the hearing because of a coincidental alleviation of head noises. This is often true of some operations, including fenestration of the semicircular canals, various operations on the mastoid and the middle ear and even removal of impacted cerumen and other substances from the external auditory meatus.

HUNTER, Philadelphia.

LIPOBLASTIC MENINGIOMA. W. TRACY HAVERFIELD and A. EARL WALKER, Arch. Surg. **42**:371 (Feb.) 1941.

A girl of 8 years was admitted with a history of transient attacks of aphasia and twitching of the right side of the face. Neurologic examination showed a somewhat irritable child who complained of headache and visual impairment. There were hyperactive reflexes in the right arm and leg and a choked disk of 2 to 3 D. Electroencephalograms showed abnormal waves from the left frontal region, and a ventriculogram confirmed the presence of a space-taking lesion in the left frontoparietal area. An osteoplastic craniotomy was performed, exposing a large, soft, yellowish, friable tumor. In the posterior part of the field the dura was intact, but anteriorly it was absent, the tumor completely replacing it. The inner table of the frontal bone was roughened, owing to invasion and erosion by

tumor. Sharp bleeding during reflection of the bone flap caused the operator to satisfy himself with removal of sufficient tumor to replace the flap and then to close the wound. Subsequently, roentgen radiation was administered to reduce the vascularity of the growth, and later two surgical procedures were necessary before removal was accomplished. The child recovered, with marked right hemiparesis, astereognosis and sensory speech defect.

Grossly, the specimens before fixation had a marked yellow color. Microscopically, all gradations from spindle cells with small vacuoles to large ballooned cells resembling adult fat cells were seen in certain areas of the tumor. The general cellular structure—sheets of meningotheliomatous cells and the arrangement of the cells in whorls and palisades—justifies the diagnosis of meningioma. Practically every cell in the tumor contained fat granules, although areas of frank degeneration were rare. The authors believe that the intracellular fat was the product of the peculiar functional activity of the mesenchymal cells from which the tumor developed. They have been unable to find the report of a similar tumor in the literature.

GRANT, Philadelphia.

FUNGOUS INFECTIONS OF THE BRAIN. GILBERT C. ANDERSON, Arch. Surg. **42**: 379 (Feb.) 1941.

Anderson reports 4 cases of fungous infection of the brain, in each of which the infection was due to a different cause: coccidiosis, saccharomycosis, actinomycosis and infection with a mycelium-producing organism.

In the first 2 cases obstructive hydrocephalus was present, being caused in the first case by occlusion of the aqueduct as a result of encephalomeningitis and in the second by a granulomatous mass in the roof of the fourth ventricle. In 1 of these cases the diagnosis was abscess of the brain, based on the clinical picture and the history of a previous pulmonary abscess. In case 3, as well, the lesion was a fulminating abscess of the brain secondary to pulmonary abscess. Actinomycosis was not suspected until the microscopic slides were studied. In the fourth case, an abscess of the left midfrontal area of the brain was localized and drained. Studies of the pus showed colonies of mycelial branching filaments and a form of mycelium-producing organism. The patient had stepped on a rusty nail four months before admission, and in the pus in this wound, which had never healed, similar organisms were found.

Although fungous infection of the brain is not a medical curiosity, it is unusual. Unfortunately, there seems to be little in the clinical history or symptoms to suggest this specific diagnosis. The prognosis is poor. Death occurred in the 4 cases described.

GRANT, Philadelphia.

Vegetative and Endocrine Systems

NEUROPSYCHIATRIC DISORDERS OCCURRING IN CUSHING'S SYNDROME. N. S. SCHLEZINGER and W. A. HORWITZ, Am. J. Psychiat. **96**:1213, 1940.

Schlezinger and Horwitz report the case of a woman aged 27 in whom a tic of the shoulder and arm developed at the age of 6 and influenza with delirium occurred at the age of 9. Regular menses were established at 14. She graduated from public school and became a stenographer. As a girl she had always been slender. At the age of 25 a change in body contour was apparent. At this time a sudden onset of depression with self condemnation occurred. Amenorrhea and urinary and fecal incontinence developed; the speech and gait changed, and the weight increased. Examination revealed round shoulders, obesity with sparing of the extremities, masklike facies, ruddy complexion with moderate cyanosis, hirsutism, abdominal striae and hypertension. Neurologic examination revealed

decomposition of movements, intention tremor, athetoid movements and cogwheel rigidity. Psychiatric examination demonstrated psychomotor retardation, poverty of thought, depression and poor retention. The dextrose tolerance curve was of a delayed type. The protein content of the spinal fluid was 97 mg. per hundred cubic centimeters; the basal metabolic rate, + 5 per cent. The cranial tables were slightly decalcified, and the shafts of the long bones showed osteoporosis. Perirenal insufflation suggested tumor of the left adrenal gland. After a laparotomy the patient died. Pathologic studies showed hyaline changes in the basophilic cells of the hypophysis, an adenoma of the left adrenal gland, encephalomalacia in the right frontal lobe and perivascular hemorrhage in the floor of the fourth ventricle. Schlezinger and Horwitz point out the similarity between the psychosis and involutional melancholia. The possibility is suggested that the Cushing syndrome in this case was of encephalitic-neuroendocrine origin. FORSTER, New Haven, Conn.

THE SPECIFIC METABOLIC PRINCIPLE OF THE PITUITARY. R. N. FEINSTEIN and E. S. GORDON, Endocrinology **27**:592 (Oct.) 1940.

That the pituitary can exert a control on heat metabolism other than by the thyrotropic factor has been indicated by the work of many investigators. Feinstein and Gordon report on studies of the effect of highly concentrated extracts of pituitary on human and rabbit metabolism as compared with the effects of similar concentrated extracts of liver.

The results obtained appear sufficient to warrant the conclusion that the pituitary contains a metabolic stimulant which significantly increases the metabolic rate both in human subjects and in rabbits. Similarly prepared extracts of liver do not appear to give a comparable response. The response to pituitary extracts is often erratic. When animals respond, they usually do so consistently and to a significant degree, but occasional animals are totally unaffected.

PALMER, Philadelphia.

BLOOD SUGAR STUDIES IN A CASE OF ADIPOSOGENITAL DYSTROPHY SHOWING CHRONIC HYPOGLYCEMIA. J. F. HART, Endocrinology **27**:759 (Nov.) 1940.

Hart reports the case of a man aged 27 with a characteristic Fröhlich's syndrome and excessive obesity (weight 369 pounds [167.4 Kg.]), pubic distribution of fat, a high sugar tolerance curve and loss of libido and potentia.

Various types of diet were tried, without success in elevating the prevailing subnormal blood sugar values to normal. A number of commercial endocrine products which are stated to have diabetogenic properties likewise failed to produce normal blood sugar values. These products included anterior pituitary extract, given orally and parenterally, solution of posterior pituitary U. S. P., preparations containing gonadotropic substances from the urine of pregnant women, insulin, testosterone propionate and oral extracts of the thyroid and adrenal glands. There was no change following the use of ammonium chloride or benzedrine sulfate. The response to the average dose of epinephrine was poor, while excessively large doses produced a delayed and marked rise in blood sugar.

The sugar tolerance curves were consistently of the low plateau type. Larger dextrose meals gave practically the same response both in the standard and in the high dextrose variation. When dextrose was given intravenously there was poor response at the one-half hour reading, and a second injection at this time produced a sudden drop in the curve. An alimentary dextrose tolerance test showed elevation of the threshold to accept almost 250 Gm. of dextrose by mouth. An intravenous Rose-Exton test showed a marked spill over the threshold with the blood sugar at 125 mg. per hundred cubic centimeters, a result which demonstrated a strong tendency on the part of the sugar metabolic mechanism to keep the blood sugar at subnormal values, even to the extent of causing a spill of sugar into the

urine at these low values. Only excessive doses of epinephrine produced any appreciable response in the sugar level of the blood. PALMER, Philadelphia.

SIMMONDS' CACHEXIA. J. C. DOANE, N. BLUMBERG and G. TEPLICK, Endocrinology **27**:766 (Nov.) 1940.

The authors report 2 cases of Simmonds' disease, the one a typical case in which histologic examination revealed almost complete absence of eosinophils of the anterior lobe of the pituitary and the other a case of apparently functional hyposecretion of the gland in which treatment with a preparation containing gonadotropic substance from the urine of pregnant women was successful.

The first case reported is that of a white woman aged 46 with the typical initial symptoms of weakness, anorexia, marked loss in weight, vomiting and dyspnea. Complete achlorhydria was present, and the initial blood pressure was 110 systolic and 60 diastolic. She became steadily worse, losing weight and becoming cachectic and senile in appearance. The blood pressure dropped to 88 systolic and 62 diastolic; the temperature became subnormal, the blood sugar fell to 60 mg. per hundred cubic centimeters and the patient died in circulatory collapse, possibly due to an unrecognized hypoglycemic reaction. Autopsy revealed microsplanchnia, absence of the right and atrophy of the left adrenal gland and atrophy of the ovaries and thyroid gland. Grossly the pituitary gland seemed normal, but histologically almost complete absence of eosinophils was noted.

Simmonds' disease may be due not only to organic destruction of the anterior lobe of the pituitary but also to functional suppression of the gland, as illustrated by the second case. In this case, that of a woman, the onset of symptoms began at the age of 22, after a psychic shock. Her signs and symptoms were typical of Simmonds' syndrome and her response to injections of an extract containing gonadotropins from the urine of pregnant women was striking and uniform. Lapse in treatment produced a relapse, while renewal of treatment produced a remission. Before treatment was initiated an assay of the urine revealed complete absence of the gonadotropic principle, whereas several months later 10 to 15 units of this substance was present. Gonadotropin assays may be valuable in differential diagnosis, especially when anorexia nervosa seems a possibility. In Simmonds' disease, gonadotropins are apparently absent in the urine.

PALMER, Philadelphia.

SYMPATHETIC ENDOCRINE SYSTEM AND VITAMIN ECONOMY. W. STEPP and F. DIEHL, Med. Klin. **36**:296 (March 15) 1940.

According to Stepp and Diehl, the endocrine glands are dependent for their function on an adequate vitamin supply. They investigated the carbohydrate metabolism from this point of view. They demonstrated in blood sugar curves following dextrose tolerance tests that it is possible to regulate abnormal functions under sympathetic-hormonal control. In cases of hypophysial insufficiency with a tendency to spontaneous hypoglycemia the blood sugar curve, following the dextrose tolerance test, could be normalized by the administration of the total vitamin B complex and of vitamin C. The formerly low apex of the curve was now higher and the abnormally deep hypoglycemic phase could be normalized. They demonstrated by means of patients with abnormal dextrose tolerance curves that the vitamin B complex has a better normalizing effect than vitamin C. The different factors of the B complex were not all equally effective; vitamin B_1 was found to be ineffective, in spite of its well known relation to the carbohydrate metabolism. The simultaneous administration of riboflavin, nicotinic acid amide and vitamin B_6 produced normalization. The authors conclude that an adequate provision of the organism with vitamins is essential for the normal functioning of the regulatory process.

J. A. M. A.

Treatment, Neurosurgery

THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS WITH VITAMIN E (TOCOPHEROLS). I. S. WECHSLER, Am. J. M. Sc. **200**:765 (Dec.) 1940.

Wechsler describes his experiences in the treatment of amyotrophic lateral sclerosis with vitamin E. The treatment consisted of the oral administration of alpha tocopherol acetate, in doses of at first 30 and later 50 mg. daily. In about one half of the cases 50 mg. of tocopherol in oil was injected intramuscularly daily. All the patients received articles of food containing vitamin E, especially lettuce, kale and whole wheat bread; two 5 grain (0.325 Gm.) pills of bile salts were given daily. Every patient received daily 2 teaspoonfuls of whole wheat germ oil. Those patients who promised recovery showed improvement fairly rapidly. The fibrillations were apt to disappear first, thus indicating a recession in the activity of the disease process. Eleven of 20 patients showed varying degrees of improvement. Two patients seem to have recovered; 4 showed marked and 5 moderate degrees of improvement. Except for the 1 man who appears to have recovered, whose illness had been of but three months' duration, the 6 patients who recovered or showed marked improvement were all women, and all were of the premenopause age. The incidence of the disease in Wechsler's series was greater in males than in females. The author calls attention to the need of revising some well established concepts as a result of his clinical studies. There are at least three, and possibly four, varieties of the amyotrophic lateral sclerosis syndrome. One occurs on the basis of inflammation, generally chronic encephalitis. Another, represented by a small group of cases, may be the result of vascular disease, possibly of syphilitic origin. These forms are presumably not the result of avitaminosis. A third, the so-called degenerative type, appears to be the result of vitamin E deprivation; in cases of this type response to vitamin E therapy may be expected. Vitamin E deficiency, probably of the alpha tocopherol factor, is one cause of amyotrophic lateral sclerosis, and the administration of vitamin E may be a specific treatment. The recognition that the absence of one vitamin may be the specific cause of a "degenerative" disease naturally leads to the assumption that other vitamins may play a role in other degenerative diseases of the nervous system. Wechsler concludes that synthetic vitamin E (i. e., alpha tocopherol) and natural vitamin E act specifically in some cases and bring about varying degrees of improvement, perhaps in inverse ratio to the age and duration of the disease process.

MICHAELS, Boston.

THE TREATMENT OF DELIRIUM TREMENS WITH INSULIN IN SUB-SHOCK DOSES. G. W. ROBINSON JR., Am. J. Psychiat. **97**:136, 1940.

Robinson has treated 24 patients with delirium tremens by two or more separate doses of 20 units of insulin covered partially by dextrose. No deaths occurred. The conditions of all the patients cleared completely, with an average period of recovery of two and four-tenths days for the whole group and of one and five-tenths days for those having no complications, such as a respiratory infection. This is compared with Kraepelin's figures for recovery (four to five days) and for the mortality rate (3 to 5 per cent). Robinson concludes that the effectiveness of the insulin results from the reestablishment of normal carbohydrate metabolism and the replacement of deficient glycogen reserves, with the obliteration of toxic intermediate products.

FORSTER, New Haven, Conn.

THE TREATMENT OF GENERAL PARESIS [DEMENTIA PARALYTICA] WITH MALARIA INDUCED BY INJECTING A STANDARD SMALL NUMBER OF PARASITES. PAUL HOCH, ERNEST KUSCH and L. T. COGGLESHALL, Am. J. Psychiat. **97**:297, 1940.

Hoch, Kusch and Coggleshall studied 32 patients with dementia paralytica treated by injecting a known number of trophozoites of Plasmodium vivax (McCoy strain). The method used was to draw blood from a donor patient, to count the

organisms in a smear and from this to compute the number of organisms per cubic centimeter of blood and then to dilute the infected blood until each cubic centimeter contained 1,000,000 organisms. Further dilutions could be made as desired. All injections were given intravenously. The patients were given injections of from 1 to 1,000 organisms. It was found that from 100 to 250 organisms was sufficient to induce clinical malaria. The incubation period seemed to be related to the number of organisms present, but the clinical course, once the incubation period was passed, was the same. When a small number of organisms are used, as in this series, the paroxysms seem milder and are better tolerated.

FORSTER, New Haven, Conn.

THE TREATMENT OF THE PARKINSONIAN SYNDROME WITH BULGARIAN BELLADONNA ROOT AND AMPHETAMINE (BENZEDRINE) SULFATE. EUGENE DAVIDOFF, EDWARD C. REIFENSTEIN JR. and NOBLE R. CHAMBERS, Am. J. Psychiat. **97**:589, 1940.

Davidoff, Reifenstein and Chambers used Bulgarian belladonna alone or in combination with amphetamine (benzedrine) sulfate in treatment of 25 patients suffering from parkinsonism, 15 of whom had the postencephalitic and 10 the arteriosclerotic type. Seven of the former and 1 of the latter group were psychotic. Treatment was carried out for periods of six to seven months. Of the 15 patients with postencephalitic parkinsonism, 8 were markedly improved and 3 were moderately improved under treatment with Bulgarian belladonna combined with amphetamine. With the same therapy 5 of the 10 patients in the arteriosclerotic group were considerably improved.

The authors concluded that of all therapies tried the best results were obtained by the combination of Bulgarian belladonna and amphetamine sulfate. Bulgarian belladonna alone was more effective than either the other alkaloids or amphetamine alone. The best results were obtained in the cases in which the disease was of shortest duration. The authors advise caution in the use of these preparations owing to their toxic reactions. They found that less Bulgarian belladonna was necessary when used together with amphetamine.

FORSTER, New Haven, Conn.

FURTHER EXPERIENCES WITH PICROTOXIN AS A CONVULSANT IN THE TREATMENT OF MENTAL ILLNESSES. ABRAHAM A. LOW, ELIZABETH MACDOUGALL, EDWARD ROSS, MANDEL SACHS and DAVID LEVITIN, Am. J. Psychiat. **97**: 686, 1940.

Low, MacDougall, Ross, Sachs and Levitin treated 102 patients with picrotoxin, 64 of them receiving picrotoxin in combination with metrazol. Picrotoxin was given in doses of 9 mg. for women and 12 mg. for men; twenty minutes later 2 cc. of a 10 per cent solution of metrazol was given. The doses were increased if necessary, and both drugs were given in increased amounts. The authors found that by use of the drugs in combination nausea and vomiting were reduced, multiple convulsions were rare, terror was absent and the seizure occurred promptly. The complications were of the same type as with either metrazol or picrotoxin.

FORSTER, New Haven, Conn.

THE TREATMENT OF MORBID SEX CRAVING WITH THE AID OF TESTOSTERONE PROPIONATE. H. S. RUBINSTEIN, H. D. SHAPIRO and WALTER FREEMAN, Am. J. Psychiat. **97**:703, 1940.

In view of the fact that large doses of testosterone propionate decrease libido in the normal male, Rubinstein, Shapiro and Freeman studied the effect of similar doses of the drug on 5 women suffering from an overintense, but normally directed, sex drive. These patients were given subcutaneously 25 mg. of testos-

terone propionate daily to every third day at times when the clinical condition warranted it. One patient who had a complicating psychosis was not permanently benefited. The other 4 showed marked but temporary improvement. Further courses of therapy were beneficial to 3 of these patients. Rubinstein, Shapiro and Freeman studied the effects of testosterone propionate on immature rats and found that it inhibits testicular and ovarian growth. The authors found no decrease in size of the pituitary gland in these animals.

FORSTER, New Haven, Conn.

PHARMACOLOGIC TREATMENT OF SCHIZOPHRENIA. S. KATZENELBOGEN and others, Ann. Int. Med. **14**:393 (Sept.) 1940.

Katzenelbogen and his colleagues present their experience with the following aspects of insulin shock therapy of schizophrenia: sensitivity to insulin, reactions following individual injections, unusual reactions (hazards) during and following individual treatments, biochemical changes, electroencephalographic patterns and therapeutic results. 1. Both men and animals may be hyposensitive or hypersensitive to insulin. The amounts necessary to provoke shock or hypoglycemic reactions varied from 25 to 400 units. Tolerance to insulin may change throughout the treatment. 2. The most common reactions of the vegetative system, profuse perspiration and abundant salivation, are usually simultaneous. The cardiovascular system responds with marked fluctuations in the pulse rate. The respiratory system usually does not show significant changes in the precomatose phase of the treatment, but in the comatose state irregular, stertorous and deep heavy breathing is frequent. More often than not the body temperature falls. General muscular relaxation or rigidity is frequent before and during the comatose state. Abolition of the corneal reflexes, weakening of the plantar reflexes or marked extension of the big toe is common during coma. The most dramatic reactions are excitement, motor restlessness, clonic convulsions and drowsiness. Usually each patient reacts along the same pattern throughout the treatments, but the quality, intensity, sequence and duration of the reactions may vary in different patients and in the same patient on different days. 3. Eight of the authors' 140 patients had unusual reactions: cardiovascular collapse, prolonged deep coma, apnea and cyanosis. Only 1 of these patients died. 4. Biochemical studies demonstrated that of the thirty-two variable constituents of the blood analyzed before the administration of insulin and during coma some showed changes during therapy beyond the limits of normal fluctuation and the errors of the methods. Serum solids had a tendency to increase, while the other constituents of the blood showed a definite decrease and then a trend toward the original level. Sugar and fermentable sugar diminish considerably and remain at a low level throughout the individual treatments. The curves for blood sugar and for inorganic phosphorus do not keep pace throughout treatment; the sugar curve remains low and the phosphorus curve rises gradually to, and in some cases, above the original level. The relation of the hypoglycemia, the reactions and the dose of insulin are not qualitatively or quantitatively consistent. 5. The 50 studies on action potentials of the brain in 17 schizophrenic patients revealed two distinct types of "brain waves." In the first (in 42 records) a fairly normal alpha rhythm, from 8 to 10 cycles per second, predominated during the earlier interval of recording. This was followed by a gradually steady decrease as the hypoglycemia progressed. Within a few hours of injection of insulin a brain wave pattern of low frequency, averaging 3 cycles per second, became predominant. There was a striking parallelism between the variations in the brain potentials and the changes in the blood sugar content. With intravenous injection of dextrose the brain wave pattern often returned to its original preinsulin type within ten minutes; with gavage the return was longer, but did not exceed thirty minutes. 6. Thirty-five of the patients were completely free from psychotic symptoms and made satisfactory adjustment outside the hospital. Twenty-five patients were improved to the extent that there was a

markedly favorable change in their behavior, with satisfactory social adjustment in the hospital and under certain favorable circumstances outside the hospital. The remaining patients showed no change. Twenty-four of the patients with remissions had been ill one year or less. J. A. M. A.

VALUE OF TRYPARSAMIDE IN THE TREATMENT OF ATROPHY OF THE OPTIC NERVE DUE TO SYPHILIS. H. SUTHERLAND-CAMPBELL, Arch. Ophth. **24**:670 (Oct.) 1940.

Amblyopia in association with primary atrophy of the optic nerve following tryparsamide therapy is of more than academic interest. Little is known concerning the mechanism of the production of amblyopia as induced either by syphilis or by the pentavalent arsenical. Toxic reactions to tryparsamide rarely occur, if the optic disks are normal and the visual fields unaffected. The presence of any abnormalities in either precludes the use of tryparsamide. As a matter of fact, and the author quotes from authoritative texts in regard to this, "The only occasion in which the use of tryparsamide is justified in optic atrophy is when the patient is already completely blind. Under these circumstances it may, of course, be used freely and is a most valuable drug for the management of the generalized neurosyphilis." SPAETH, Philadelphia.

THE USE OF CURARE IN MODIFYING METRAZOL THERAPY. R. W. GRAY, F. L. SPRADLING and A. H. FECHNER, Psychiatric Quart. **15**:159 (Jan.) 1941.

The authors describe a technic of metrazol therapy with the use of curare. They employed an aqueous solution of curare, each cubic centimeter of which has a potency equivalent to that of 10 mg. of the crude drug. A dose of 1 cc. of the curare preparation per 20 pounds (9.1 Kg.) of body weight was given three minutes before the injection of metrazol. The result was a typical metrazol convulsion with marked decrease in violence of the tonic and clonic phases. Little disturbance of blood pressure occurred, and postconvulsive excitement was reduced. In 3 cases respiratory depression required administration of prostigmine methylsulfate and artificial respiration. The results with controls were not enumerated. Fifty patients were given combined therapy, averaging nine and seven-tenths treatments per patient. All were examined before and after treatment, but only a small number had roentgenograms of the spine after treatment. No injuries were found. The therapeutic results were considered comparable to those secured with unmodified metrazol therapy. SIMON, Worcester, Mass.

AMPHETAMINE (BENZEDRINE) SULFATE. A. C. IVY and L. R. KRASNO, War Med. **1**:15 (Jan.) 1941.

Ivy and Krasno have reviewed all the literature on the pharmacology of amphetamine (benzedrine). They assert that amphetamine sulfate is a useful drug when administered under the direction and supervision of a physician. Its usefulness in the management of narcolepsy, postencephalitic parkinsonism and mental depression is well established. Its use to dispel sleepiness in normal persons is not advisable because of the possibility of objectionable side reactions and habit formation. In most persons it promotes wakefulness and a feeling of well-being and decreases fatigue. It tends to improve psychomotor activities. The effect of the drug on the performances of persons whose duties require highly technical maneuvers and the manifestation of specialized judgments in the presence of anxiety and on the physiologic processes and performance of persons who have worked hard all day and must continue to work hard all night have not been adequately studied.

Caution in the use of the drug is required because some people are susceptible. The initial dose should not be greater than 10 mg., or better still 5 mg.

PEARSON, Philadelphia.

Congenital Anomalies

DIPLOMYELIA. R. YORKE HERREN and JESSE E. EDWARDS, Arch. Path. **30**:1203 (Dec.) 1940.

Herren and Edwards report the case of a 23 year old woman with diplomyelia involving the lower part of the spinal cord. There was associated spina bifida. A bony process in the midline extending to the arches of the eleventh thoracic vertebra divided the vertebral canal in two. There were clubfoot on the left, absence of knee and ankle jerks and coldness and cyanosis of the left foot with intermittent trophic ulcers. Death was due to a neoplasm involving each thalamus, diagnosed as glioma.

WINKELMAN, Philadelphia.

FAMILIAL PES CAVUS AND ABSENT TENDON-JERKS: ITS RELATIONSHIP WITH FRIEDREICH'S DISEASE AND PERONEAL MUSCULAR ATROPHY. JOHN D. SPILLANE, Brain **63**:275, 1941.

Spillane made a study of a family group in which 21 members presented signs of degeneration of the spinal cord. Of these, 16 had the syndrome of Roussy and Lévy, consisting of bilateral pes cavus, absence of tendon jerks and difficulty in walking. Four of the 16 patients showed as well an explosive type of dysarthria. The abnormality usually becomes evident in infancy, with delay in learning to walk, clumsiness and frequent falls. The foot deformity develops early during childhood. Running and jumping become impossible. In most of the 16 cases described slight clumsiness of the hands and atrophy of the thenar and hypothenar eminences were observed. The condition usually progresses slowly during adult life, and a slight amount of functional adaptation may occur.

Three of the 21 patients presented a typical picture of Charcot-Marie-Tooth muscular atrophy. Another, with a fairly typical case of Friedreich's disease, showed marked kyphoscoliosis, bilateral pes cavus, absence of knee and ankle jerks and extensor plantar reflexes.

Thus, in one family group there occurred cases of the syndrome of Roussy and Lévy, of Friedreich's disease and of the Charcot-Marie-Tooth type of muscular atrophy. In the absence of pathologic evidence, Spillane concludes that the syndrome of Roussy and Lévy represents a subgroup of the heredofamilial degenerations of the spinal cord and cerebellum, of which Friedreich's disease and the Charcot-Marie-Tooth muscular atrophy are fully developed forms.

MASLAND, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

LEON H. CORNWALL, M.D., *President, in the Chair*

Regular Meeting, Feb. 4, 1941

Unusual Mental Syndrome in a Case of Tumor of the Frontal Lobe.
DR. ISRAEL STRAUSS.

A white man aged 46, a shoemaker, was admitted to the Morrisania City Hospital on July 28, 1939. In March 1939 he began to complain of blurring of vision and severe frontal headaches. He spoke loudly, as though he were having difficulty with his hearing. He had attacks of dizziness and frequently walked into things. He was also becoming irritable. The past history was essentially irrelevant.

Examination revealed euphoria, slurring of speech, incoherence, disorientation in all spheres and poor memory for recent events. The temperature was 102 F. and the pulse 90.

Neurologic Examination.—The right pupil was slightly larger than the left, and both reacted well to light and in accommodation; the fundi were normal. There was slight mimetic weakness of the right side of the face. The deep reflexes were preserved, being slightly more active in the left lower extremity. There were coarse tremor of the upper extremities, loss of associated movements in closing the hands and absence of abdominal and pathologic reflexes.

Lumbar puncture revealed clear fluid, with an initial pressure of 160 mm., and no manometric block; the Pandy and Wassermann reactions were negative; the colloidal gold curve was flat; there were 64 mg. of sugar per hundred cubic centimeters and 28 lymphocytes per cubic millimeter.

The roentgenogram of the skull revealed nothing abnormal.

The patient showed marked emotional instability, swinging from apathy to marked excitement. Incontinence of the sphincters was present. Nineteen days after admission the mental symptoms cleared, with persistence of elation. Lumbar puncture just prior to discharge, thirty-seven days after admission, showed an initial pressure of 115 mm., with no cells. He was discharged as improved except for persistent emotional lability. A tentative diagnosis of encephalitis was made.

Six months after discharge (September 1940) he was readmitted because of loss of weight, ready fatigability, severe right-sided headache, change of personality and impairment of efficiency at his work; he spoke and acted queerly, often staring vacantly during conversations. Pathologic somnolence was evidenced; he often became dizzy, with a tendency to fall backward; there was gross tremor of both hands. Neurologic examination revealed nothing abnormal.

The patient presented a picture of marked deterioration of personality; he yawned frequently and smiled fatuously; questions had to be repeated constantly. There were marked memory defect, especially for recent events, disorientation, no insight into the morbid nature of his recent experiences and behavior and incontinence of urine and feces.

Lumbar puncture revealed clear fluid, with an initial pressure of 210 mm. of water; manometric studies gave normal results; the total protein content of the spinal fluid was 76 mg. per hundred cubic centimeters; a qualitative test revealed sugar; the Wassermann reaction was negative; the colloidal gold curve was flat;

the Ayala index was 5.7. Lumbar puncture repeated sixteen days later gave similar results, except for an initial pressure of 90 mm. of water.

The results of a pneumoencephalographic examination were unsatisfactory; air insufflation was not again attempted, since the patient showed significant improvement immediately after the procedure: The confusion cleared, and the behavior became more normal; rapport was definitely more satisfactory; restlessness and hyperactivity were much less pronounced.

The dominant mental content at the time was a circumscribed delusion that a group of people had schemed against him and had brought him to his present plight by rubbing drugs on his genitals; he heard these people express the intention of killing him; affective responses were inadequate as he told of these delusional experiences.

A second pneumoencephalogram showed complete obliteration of the left anterior horn; the right anterior horn was displaced superiorly and posteriorly by a large tumor, in which calcification could be noted. A week after the second pneumoencephalogram, as after the first, the patient stated that he was better, that "it was all imagination." Repeated neurologic examinations gave normal results.

On Oct. 30, 1940 a left craniotomy, performed by Dr. Sidney W. Gross, revealed a large tumor having the gross appearance of a meningioma, which occupied the left frontal pole and extended backward 8 cm. from the tip of the lobe, subcortically, in all directions. Most of the tumor was removed. Microscopic examination showed a transitional cell glioma.

Six weeks after operation the sensorium was clear; there was no evidence of mental enfeeblement or amnesia for the previous confusional state, but the patient did not as yet show complete insight. Four months after operation there were no objective symptoms of any neurologic disorder; orientation was good; there was no intellectual deficiency; the man worked daily in a store conducted by him and his wife; he had unusual insight into his previous mental state, although he persisted in the idea that two nurses had manipulated his genitals and had infected his penis. No amount of persuasion would make him admit the possibility of this idea being false or delusional.

Dysmorphopsia During the Course of Sulfanilamide Therapy. Dr. Hyman Weitzen (by invitation).

A woman aged 25 was admitted to the gynecologic service at the Morrisania City Hospital with evidence of a pelvic infection, which appeared fifteen days after childbirth. On admission the temperature was 103 F. and the pulse rate was 120. She was placed under sulfanilamide therapy, with an initial dose of 2.6 Gm. This was followed by 1 Gm. every four hours, with equal amounts of sodium bicarbonate. Ergonovine malleate, 0.002 Gm., was given by hypodermic injection three times a day, with supportive treatment in the form of intravenous therapy and small transfusions. Three days after admission, after having received a total of 8.6 Gm. of sulfanilamide, she began to complain of severe headache and blurring of vision. For two days she had peculiar visual experiences. She stated that her own fingers and toes appeared unusually short and pudgy. At times the fingers seemed to show an angular distortion, as if they were broken in the middle. She also stated that when she held her hands in front of her one or two fingers looked nearer to her than the others. She also noted that objects in the hospital looked unusually thin, with curvilinear distortions, such as are often seen in trick mirrors. On a few occasions during this two day period she noted transitory telopsia and micropsia. People did not look distorted to her. When she was asked to look at pictures she did not describe similar distortions of vision. She recognized all objects placed before her. There was no alexia, agraphia, apraxia, finger agnosia or discalculia. Spatial orientation was intact. Geometric patterns were copied without any distortion. Results of mental examination were entirely

normal. No visual field defect was noted. Visual acuity was diminished to 10/200 in the right eye, with correction to 20/40, and 15/200 in the left, with correction to 20/70. The fundi were normal. Examination of the spinal fluid showed an initial pressure of 140 mm. of water. There were no cells and no increase in protein or sugar.

In addition to probable direct involvement of the nerve itself or the retinal cells, as evidenced by the blurring of vision during this two day period, there was cerebral metamorphopsia, which was probably due to sulfanilamide. This metamorphopsia was considered cerebral, particularly because of the peculiar dissociation between objects and environment. If the distortion of visual images were due to retinal edema, all objects should have shown similar changes.

DISCUSSION

DR. LEON H. CORNWALL: Within the last two months I have seen something similar to the condition that has been described. The dysmorphopsia was not quite so marked, but it was accompanied by mild hallucinosis. It occurred in a member of my own family while under treatment with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate). It was amusing to hear the descriptions that were given of the auditory and visual hallucinations and the visual distortion.

Recurrent Pneumococcic Meningitis (Type II). DR. F. C. ANSANELLI (by invitation.)

I believe there is no report in the literature of a case of recurrent pneumococcic meningitis caused by an organism of the same type as proved by culture. Craddock and Bowers seem to have reported the first case of recurrent pneumococcic meningitis (*J. A. M. A.* **116**:296-298 [Jan. 25] 1941); yet in their case no one type of pneumococcus was found twice. The lack of reports of recurrent pneumococcic meningitis may be due to the fact that effective therapy with sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) was not introduced until 1938. Since then increasing reports of cases have appeared, such as those by Reid, Robertson and Hodes, in which single attacks of meningitis have been cured by sulfapyridine.

In the case reported here there were four attacks of pneumococcic meningitis type II treated with serum in addition to sulfapyridine and its sodium salt. The patient was a Spanish salesman who, three days after recovery from pneumonia, on February 27, presented himself for readmission, with the complaint of pains in the head and vomiting. Examination revealed a temperature of 103 F., nuchal rigidity and bilateral Kernig and Brudzinski signs. Studies of the spinal fluid revealed the findings characteristic of purulent meningitis, a positive reaction to the Neufeld test and Pneumococcus type II on culture. The patient was treated immediately with pneumococcus type II serum, intravenous injections of sulfapyridine sodium and oral administration of sulfapyridine. The lowest concentration of sulfapyridine in the blood and spinal fluid was 11 mg. per hundred cubic centimeters and the highest 32.4 and 23 mg., respectively. On March 5 the patient had recovered.

Recurrent attacks occurred between March 25 and April 1, April 9 and 15 and April 24 and May 5, the patient being well in the intervening periods, with the spinal fluid clear and the sugar content normal. He was discharged as cured on June 2, 1940 and continues to be well seven months later. In all the attacks serum and sulfapyridine were employed, except in the second, in which oral administration of sulfapyridine and sulfapyridine sodium sufficed. In the fourth attack the patient did not respond well to chemotherapy, and it was not until pneumococcus serum was given intraspinally that he became asymptomatic. A satisfactory level of sulfapyridine in the blood and spinal fluid was always main-

tained. Five days after the last attack there was a temperature of 100 to 101 F. The patient refused to have a spinal puncture. For a possible existing focus, roentgen therapy was given to the cerebrospinal portions. The entire treatment had no associated toxic reactions or complications.

A focus was most likely the cause of the recurrent attacks. Detailed investigation did not reveal such a focus, but it is likely that the reservoir of infection was in the nature of one or more small meningeal loculations of exudate.

Atypical Syndrome with Herniation of the Nucleus Pulposus. Dr. Henry Wigderson (by invitation).

A 15 year old white boy was admitted to the Morrisania City Hospital on Feb. 10, 1939 with complaints of pain on bending, weakness of the legs and difficulty in walking, all of about three weeks' duration.

He had received an injury to his back when he fell a distance of 10 feet (0.3 meter) from the limb of a tree on which he had been climbing, and in January 1939, while playing, he was struck in the same region. After this he had pain in the back, but was not incapacitated. Two weeks later, while exercising in a gymnasium, he felt something snap in his back. After this he had constant pain in the lower part of his back and progressive weakness of his legs.

Physical examination on admission revealed marked weakness of both lower extremities, presence of the Lasègue sign bilaterally, prominence of the eleventh and twelfth dorsal spinous processes, spasm of the erector spinae muscles, tenderness over the spinous process of the twelfth dorsal vertebra, absence of the patellar reflex and an active achilles reflex on both sides. There was hypesthesia in the sacral segments. The abdominal reflexes were active. There was no tenderness of the calf muscles. Roentgenograms of the dorsolumbar portion of the spine revealed no abnormality.

On February 19 a lumbar puncture was attempted, but no fluid was obtained. After the attempted puncture, flaccid paraplegia developed, with complete areflexia of both lower extremities. There were bilateral impairment of vibratory sensation in the lower extremities, more marked on the right, and impairment of position sense in the toes of the right foot. Touch was impaired in the distal portion of the right lower extremity. There was hypalgesia on the right from the third lumbar to the second sacral segment; on the left the fourth and fifth lumbar segments were involved. All the abdominal reflexes were active. There was no Beevor sign. There was no response to plantar stimulation. Some difficulty in urination also followed the attempted puncture.

The following day a lumbar puncture was done in the second lumbar interspace. The initial pressure was 80 mm. of water. There was no response to jugular pressure. Three cubic centimeters of xanthochromic fluid was removed. The fluid pressure was zero. The next day a cisternal puncture was done, and 2 cc. of iodized poppyseed oil was injected. There was complete arrest of the oil opposite the first lumbar interspace.

On February 22 lumbar laminectomy was performed. The cord opposite the first lumbar interspace was seen to be angulated posteriorly, and a herniated nucleus pulposus was removed through a transdural approach. Microscopically, the specimen consisted of annulus fibrosus and nucleus pulposus, which showed degenerative changes.

The postoperative course was uneventful, but return of function was slow. There was no sphincteric disturbance at any time. Five weeks after operation the patient was beginning to move his feet and toes. There was slight diminution of touch and pain sensations in the acral portions of the legs. Vibratory and position senses were markedly impaired. In three months he was able to walk with the aid of crutches.

At present, almost two years after operation, he is able to walk without braces and can walk up to a half-mile (0.8 kilometer) without tiring. There are atrophy of the calf muscles and weakness of the peroneal muscles bilaterally. The knee and ankle jerks are absent on both sides. Position sense is normal. Vibratory sensation is impaired in both feet. There is slight diminution in the perception of superficial touch and pain sensations below the first lumbar segment.

The history of repeated trauma to the back is common in cases of this injury. However, several features in this case are unusual in the clinical picture of rupture of the intervertebral disk. The age of the patient, 15 years, is lower than that of most patients with such a lesion. In a series of 100 cases reported by Love, the average age was 40 and only 1 case occurred in the second decade of life. Rupture of the intervertebral disk at the first lumbar interspace occurred in only 2 per cent of the reported cases. In many cases varying degrees of weakness are shown, but in very few has paraplegia been reported.

The complete arrest of the iodized poppyseed oil is also unusual. In most cases there is some deformity of the column of oil at the level of the ruptured disk, but not a complete arrest.

The designation of this case as atypical indicates the increase in knowledge of the clinical picture of ruptured disk during the past few years. Prior to 1933 about a dozen cases of protrusion in the lumbar region had been reported. In reviewing these cases it was found that the present case is similar to many of them. Since ruptured disk with compression of only one or two nerve roots is now recognized, the more extensive lesions, in which the cord or all the roots of the cauda equina are involved, are considered atypical. So what is now regarded as atypical was essentially the only form recognized prior to 1934.

Several authors have shown that herniation of the nucleus pulposus may follow a lumbar puncture in which the needle is inserted too far and damages the posterior longitudinal ligament. In the present case paraplegia developed after an attempted puncture. No fluid was obtained, and I think it fair to assume that the needle did not enter the spinal canal. In this case the mechanism seems apparent. The patient had a partially protruded disk, and when the back was flexed, more, if not all, of the disk was forced out of the intervertebral space.

In cases in which symptoms of a ruptured disk follow spinal puncture, flexion of the spine may be more important in producing such symptoms than the puncture.

Sciatic Pain as the Initial Symptom of Subarachnoid Hemorrhage. Dr. Nathan Savitsky and Dr. Israel Strauss.

Sciatic pain is known to be the initial symptom of spinal subarachnoid hemorrhage. There has not been enough emphasis on the occurrence of such pain when the source of subarachnoid bleeding is in the intracranial cavity. Two cases are reported in which sciatic pain appeared at the onset of subarachnoid hemorrhage. The first case is that of a 15 year old boy who complained of sciatic pain on the left side of five days' duration. On admission to the hospital he was referred to an orthopedic clinic, from which he was discharged to his home. He later became acutely ill; he was drowsy and had a stiff neck. A Kernig sign was present bilaterally. The spinal fluid was bloody, with a supernatant xanthochromic layer. The second case was that of a 22 year old woman who was admitted with a history of pain in the posterior aspect of the right lower extremity, of eight months' duration. The pain varied in intensity, with occasional severe exacerbations. A few months before admission she complained of sudden blurring of vision. On the first admission a diagnosis of lumbosacral radiculitis was made. She continued to complain of pain after her discharge from the hospital and was readmitted later, when diminution of visual acuity became rather marked. On the second admission she showed papilledema of 1.5 to 2 D. Sensory changes in the lumbosacral dermatomes which had been previously present were no longer demonstrable. Operation (Dr. Ira Cohen) disclosed a hemangioendotheliomatous

cavernoma in the left frontal lobe. After the operation the sciatic pain disappeared. Pain in the distribution of the sciatic nerve was the presenting symptom in both cases. The cause of such pain is probably irritation of the spinal roots in the lumbosacral region. Acute and chronic bleeding into the subarachnoid space can cause pain in the lower limbs, and the source of this bleeding may be intracranial.

Statistical Control Studies in Neurology. DR. NATHAN SAVITSKY and DR. M. J. MADONICK (by invitation).

The purpose of this study was to gather data on the incidence of a few neurologic signs in control groups of patients. The Babinski sign, the pronator sign, nerve deafness and distress with conjugate deviation of the eyes were studied in 2,500 patients at the Morrisania City Hospital who were admitted for diseases other than those of a nervous or mental type. In addition, a group was studied consisting of 800 patients with a diagnosis of neurosis, 800 with injuries to the head and 704 military draftees. All the examinations were conducted personally. Data were not taken from hospital charts.

A positive Babinski sign was found in 4.28 per cent of the 2,500 hospital control patients and in 4.75 per cent of the patients with head injuries. An equivocal Babinski sign was not considered positive. There was no question about the pathologic nature of the plantar responses. The first 800 consecutive hospital control subjects showed an incidence of 3.7 per cent. There was no significant statistical difference between the 3.7 per cent for the hospital control group and the 4.75 per cent for the group of patients with head injuries. The actual difference between these two values is less than three times its probable error. Additional proof that this 3.7 per cent is a result of chance, and is not due to a real difference between the two groups, is the fact that the collection of further data resulted in closer approximation of the values for the two groups. The relatively high incidence in the control group may be partly due to the high proportion of persons over 50 years of age. There were twice as many persons over 50 in the control group as in the group with head injuries. Further confirmation of the theory that age is a factor was the finding of a positive Babinski sign in 1.15 per cent of the hospital control patients between 21 and 25 years of age and in 1.27 per cent of 704 draftees. There arises, of course, the problem of the probable incidence of this pathologic sign in large groups of employees. It is suggested that wherever such large groups of employees exist it is worth while to submit them to an examination before permitting them to work.

The tendency of patients with chorea to hyperpronate the outstretched upper limbs has been described by Wilson. It was found to be present in 91 per cent of 71 patients with all types of chorea and in 22 per cent of the 2,500 hospital control patients. The sign was present in 72.6 per cent of 252 patients with all types of rheumatic disease (active and inactive rheumatic fever). It was present in 16 per cent of 2,258 control subjects without rheumatic fever. It was positive in 42 per cent of patients below 19 years of age and in 17 per cent above 19. Age apparently is not a factor, for 29 per cent of all the patients in the hospital control series below 19 years of age and 8 per cent of those above had rheumatic fever. The very high incidence of the pronator sign in patients with rheumatic fever without chorea suggests the probability of mild cerebral involvement in a relatively high percentage of cases. A similar high incidence was not found in any other group.

An attempt was made to evaluate the usual simple method of determining nerve deafness. The difference in auditory acuity on the two sides was determined. The patient was considered to have nerve deafness when there was diminution of auditory acuity, lateralization of the Weber sign to the opposite side and quantitative diminution of bone conduction on the affected side. For the purpose of this study, patients who showed changes in the ear drums were included in both groups.

Comparison was made between 800 patients with injuries to the head and 800 with conditions diagnosed as neuroses. Nerve deafness was found in 10.25 per cent of those with head injuries and in 1.25 per cent of those with conditions diagnosed as neuroses. This difference between the two groups is statistically significant. It indicates that the method as used has definite clinical value, and points to probable injury in the inner ear.

The incidence of distress with conjugate gaze was studied in the 800 persons with injuries to the head and in the 800 patients with disorders diagnosed as neuroses. The patients were examined in exactly the same way and by the same examiner. Patients were not asked at first to tell their subjective experiences during conjugate gaze. If they showed evident distress during conjugate gaze they were asked to describe the nature of the distress. Cases of paresis of conjugate gaze were not included. Of 800 patients with head injuries, 4.6 per cent showed distress with conjugate gaze. Only 1 (0.12 per cent) of 800 patients with conditions diagnosed as neuroses showed this positive symptom.

DISCUSSION

DR MORRIS B. BENDER: Have the authors made any studies on the persistent and the transient type of nystagmus?

DR. NATHAN SAVITSKY: Nystagmus is one of the subjects in which we have been interested. Nystagmus is found rarely in cases of injury to the head, even with definite evidence of injury to the brain stem, and when present is usually transitory. We found practically no nystagmus, except in 2 or 3 instances of congenital nystagmus, in our group of patients with disorders diagnosed as neuroses.

DR. MORRIS B. BENDER: What is the incidence of transient nystagmus? Scott (*Proc. Roy. Soc. Med.* [*Sect. Neurol.*] **7**:40 1914) made a series of observations on a group (500) of so-called normal subjects, and found the transient type to be present in 20 per cent when the visual axes deviated beyond the range of binocular vision.

DR. NATHAN SAVITSKY: We cannot corroborate such a high incidence of nystagmus; it depends on what he called nystagmus. If he included the so-called physiologic nystagmus, we can report the incidence to be as high as 20 per cent. Nystagmus which could be considered clinically significant was not found in either group.

The Electroencephalogram of Normal Children: Effect of Hyperventilation. DR. NORMAN Q. BRILL and DR. HERTA SEIDEMANN (by invitation).

The electroencephalograms of 100 normal children were studied. None of the subjects had a family history of epilepsy. The age range was from 4 to 14 years.

Above the age of 9½ years alpha frequencies below 8 per second were not observed, while below this age alpha frequencies of 6 to 8 per second were seen. In addition, there was an abrupt decrease in the incidence of slow waves (2 to 6 per second) above this age. This seemed, therefore, to be a critical age with regard to the electroencephalogram.

There was a tendency for the alpha activity to become more rapid, and thus approach the adult level, with advancing years. Associated with this was a definite trend toward better regulation of the alpha activity. These findings are in agreement with those of Lindsley and Smith.

The effect of hyperventilation was observed. The younger children showed a greater tendency to dysrhythmias during hyperventilation than did the older ones, especially when slow activity was present in the spontaneous record. In 40 per cent of the children between the ages of 4 and 6 years abnormal rhythms developed, while in only 9 per cent of the 10 to 12 year group did such changes appear. The curve of diminishing trend followed almost a straight line, except for a slight

rise in the 12 to 13 year period. As a corollary, it was seen that the tendency to maintain a normal record during hyperventilation increased with advancing age, except for a slight decrease in the 12 to 14 year group. Previous studies have shown that dysrhythmias rarely develop in normal adults during hyperventilation.

The dysrhythmia observed in the normal children was similar to the dysrhythmia seen in the spontaneous records and in those taken during hyperventilation in epileptic patients. The question, therefore, whether it is to be considered abnormal in children has frequently arisen. Because of its high incidence, particularly in the younger children, it cannot be considered abnormal. It does seem to represent, however, a tendency to the convulsive state which is gradually outgrown. This is in accord with the clinical experience that the convulsive threshold diminishes with advancing age. It is possible that the children who continue to show the dysrhythmia are the ones from whom the adult epileptic population is derived.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

LINUS J. FOSTER, M.D., *President, in the Chair*

Regular Meeting, April 24, 1941

Vitamin E and Alpha Tocopherol Therapy of Neuromuscular and Muscular Disorders. DR. RUSSELL N. DE JONG, Ann Arbor, Mich.

The use of alpha tocopherol and wheat germ oil in the treatment of 19 patients with amyotrophic lateral sclerosis, 1 with amyotrophic lateral sclerosis associated with syphilis, 5 with progressive spinal muscular atrophy, 8 with pseudohypertrophic muscular dystrophy and 2 patients with recent, extensive poliomyelitis is reported. Large doses, often as much as 240 mg. of alpha tocopherol daily by intramuscular injection, have failed to bring about definite objective improvement in any case. Some patients noted a slight decrease in muscular fibrillations; others noted a feeling of well-being with slight subjective gain in strength, which was only temporary, but in none was there evidence of restoration of atrophic muscles, improvement in speech or deglutition or change in the reflexes. The course of the disease progressed in most instances. Definite toxic reactions were observed in 2 patients and questionable ones in 2 others. The beneficial effects of alpha tocopherol therapy that have been reported by other observers were not confirmed.

Intracranial Aneurysm. DR. CARL F. LIST, Ann Arbor, Mich.

Early recognition and accurate localization of intracranial aneurysm are necessary for any surgical treatment. The most common intracranial aneurysm arises from a congenital anomaly of the arterial wall. Saccular aneurysm may develop to such size as to compress adjacent structures. Intracranial aneurysm arising from the circle of Willis tends to enlarge by intermittent miliary leakage, but this does not preclude eventual rupture. (There followed a discussion of the problems to be confronted in cases of intracranial aneurysm.)

Prognostic Factors in Schizophrenia. DR. JULIUS M. WALLNER, Ann Arbor, Mich.

The prevailing concept of schizophrenia as a group of syndromes, related in symptomatology but differing in etiology, course and prognosis, is presented. For better definition of the members of this group, and more valid appraisal of the therapeutic regimens, it is urged that careful and intensive studies be made of individual patients on whom adequate follow-up observation can be assured.

Of particular interest are those patients the course of whose illness is episodic or chronic but deteriorating. The onset may be acute or insidious; the habitus is rarely pyknic; the personality type is usually schizoid; capacity for affective expression is reduced, but subjective complaints of being in a "turmoil" or "tempest" are not uncommon. Early in the illness the patient may be aware of a change in affective relations and be puzzled by difficulty in concentration and thinking.

Loss of decency in the acute state, with denudative and smearing tendencies, may be noted. Later, somatic hallucinations and feelings of unreality and depersonalization and of influence are common. If, in addition to some of these changes, thinking disturbances in a state of relative clearmindedness are demonstrable, the clinical picture is that of the so-called process schizophrenia and the prognosis is grave.

(The contributions of men interested in thinking disturbances were briefly reviewed [Bleuler, Piaget, Storch, Vigotsky, Cameron, Goldstein, Bolles, Weigel and Halstead].)

Artistic Productions in a Case of Schizophrenia. Dr. Floyd O. Due, Ann Arbor, Mich.

The paintings of M. F., a 26 year old single woman of some artistic training, are presented by means of colored lantern slides. The paintings were produced during hospitalization in the Neuropsychiatric Institute, while the patient was experiencing her second acute attack of paranoid and catatonic schizophrenia. The first acute attack, necessitating care in the Cleveland Psychopathic Hospital, occurred in 1934. The patient had been discharged as markedly improved before the presentation and was effecting a satisfactory social and work adjustment.

The symbolism, mode of expression, attention to detail and utilization of colors are demonstrated to have varied with the clinical status. Improvement was accompanied by technical advances and restraint in symbolization, while clinical recession was characterized by more primitive modes of expression.

It is considered that the productions should be comparable to dreams, and a free association technic was utilized to reveal latent content. Disappointment, death and reincarnation are frequent themes of the paintings, while snakes, swans and dismantled flowers are frequent symbols.

The associations revealed an unresolved oedipus complex with tremendous unconscious hostility toward her mother, who had rejected her. Prominent throughout was the expression of her "masculine protest," with frequent allusions to the importance of the penis. There had resulted a conscious bisexuality, which prevented the achievement of sexual gratifications, as well as the attainment of life goals.

It is concluded that the utilization of artistic productions can lead to a deeper insight into the psychodynamic structure of a patient's illness. The artistic expression itself had afforded a sublimation process, with frequent abreactions to certain affective components that may have otherwise remained repressed. As such, the expression, along with increasing insight following associations and interpretations, was an important element in the clinical improvement. Furthermore, it is demonstrated that the mode of expression, composition and symbolization can be utilized as an index to the clinical status of the patient.